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VOL. 36 July, 1948 No. 1

Original Communications

NEW CONTRIBUTIONS TO THE STUDY OF THE INTRACAVITY POTENTIAL IN CASES OF RIGHT BUNDLE BRANCH BLOCK IN THE HUMAN HEART

DEMETRIO SODI-PALLARES, M.D., PABLO THOMSEN, M.D., AND JORGE SOBERÓN, M.D.

MEXICO D. F., MEXICO

A PAPER entitled "Comparative Study of the Intracavity Potential in Man and in Dog," was presented by several of us[1] at the Second Inter-American Congress of Cardiology. In it the electrodes and the technique used for the study of the intracavity potential in man as well as in animals were described. It was also shown that normal tracings, tracings showing ventricular extrasystoles, and tracings showing bundle branch block both in dogs and in men were remarkably similar. A number of other conditions difficult to produce in animals were also studied in man.

In this paper we present the data recently obtained regarding intracavity potential in right bundle branch block. In the paper on intracavity leads[1] we stated that "The intra-auricular QRS complexes are similar to those found in right ventricular hypertrophy, with a definite preponderence of positive deflections. At the upper part of the auricle, the late R is broad and slurred like that found in Lead V_R in the same condition. At the lower part of the auricle the late R is still predominant but less slurred. The tracing is strikingly similar to that found in experimentally produced block in the dog. One case had the same shape in Lead V_6 and in the tracing obtained from the inferior vena cava. The intraventricular tracing shows diphasic QRS complexes (of the RS type) with negative T wave, more or less like that found in animals in the right ventricular cavity, in experimental conditions for the same type of block and left ventricular extrasystoles."

From the National Institute of Cardiology of Mexico.
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THE ELECTROCARDIOGRAPHIC FEATURES OF RIGHT BUNDLE BRANCH BLOCK

Precordial leads using Wilson's central terminal easily furnish diagnostic evidence of right bundle branch block. In right precordial Leads V_1 and V_2, the ventricular complex most commonly assumes the rsR type with negative T wave. Sometimes, especially if there is an associated anteroseptal infarct, the small positive initial deflection may disappear and the complex becomes one of the qR type. At other times, the ventricular complex is purely positive (R wave) and has an initial portion with a notch of varying depth. For this reason, the general morphology is similar to that of the complex first described (rsR).

The small initial R wave has been attributed to the activation of the septum. The S wave which follows the small R wave or the Q wave, if the ventricular complex is of the qR type, is considered to be produced by the vectorial forces incident to the activation of the free wall of the left ventricle. The late R wave of greater voltage seems to be produced by the late activation of the free wall of the right ventricle.

In the left precordial Leads V_5 and V_6, the complexes are of the RS or qRS type. The S wave is wide and slurred in the majority of instances. When there is a Q wave it appears to have the same significance as the initial R wave in Leads V_1 and V_2, that is, they are related to septal forces which produce them. The positive deflection corresponds to the activation of the free wall of the left ventricle and the S wave to the activation of the free wall of the right ventricle.

These interpretations have been accepted by all those who routinely work with the central terminal. Since we have been working on intracavity potential, we have become interested in the meaning of the different precordial deflections and we wish to emphasize certain points in cases of right bundle branch block.

The duration of QRS complex in right bundle branch block is 0.04 to 0.05 second longer than in normal tracings. This is easily proven experimentally since QRS becomes wider by 0.04 to 0.05 second after sectioning of the right bundle branch in the dog. It is thought that after cutting the right branch, the impulse of activation crosses the septum from left to right and is transmitted through muscular fibers rather than the network of Purkinje. Intraventricular tracings support this view. The normal tracing is of the rS type,[1] and the peak of R is inscribed about 0.01-0.02 second after the beginning of the ventricular complex. In animals in which the right branch has been severed, the tracing is of the RS type[1] and the peak of the positive deflection is inscribed about 0.045 second after the beginning of the same ventricular complex. Tracings obtained from human subjects show similar time relations (Fig. 1,*A*) and even more delay (Fig. 2,*D* and *E*), which could be interpreted to suggest the presence of myocardial changes of the septum which would further retard the passage of the stimulus.

It is quite probable that in normal subjects the upper portion of the interventricular septum is activated from left to right early in the QRS interval; in this way it is easy to explain the initial positive wave of the normal right intraventricular tracing, which records a higher voltage when the exploring electrode is closer to the upper portions of the septum.[2] Lewis has emphasized that in the ventricle the superior septal portions are the first to be activated.

There is no reason to believe that right bundle branch block alters the early activation of the upper portion of the septum, therefore one must suspect two different phases in the activation of the interventricular septum in right bundle branch block: first, an early phase, corresponding to activation of the upper

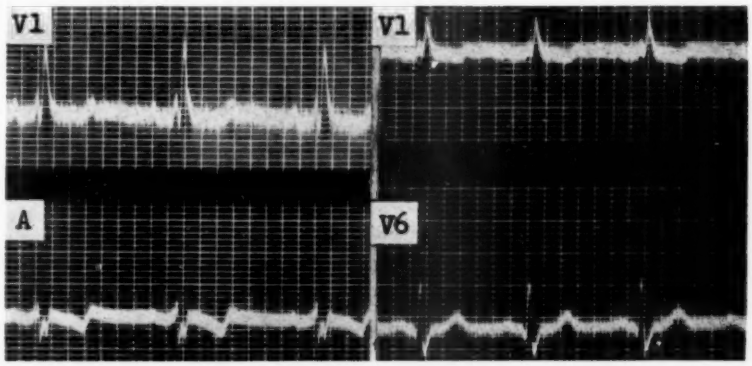

Fig. 1.—Right bundle branch block. *A*, Unipolar intracavity tracing with the exploring electrode inside the right ventricle. The other tracings correspond to precordial leads taken with a central terminal. Time in 0.10 second.

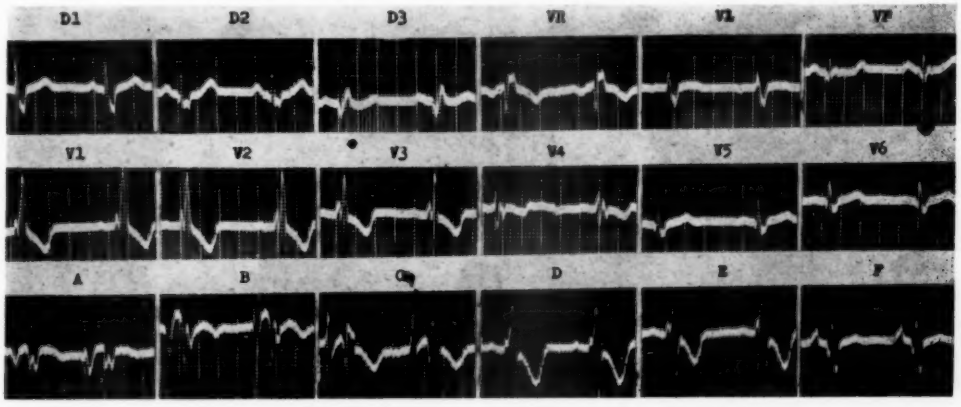

Fig. 2.—Right bundle branch block. Intracavity unipolar leads taken: *A*, in superior vena cava; *B*, at high auricular level near the sinus node; *C*, at midauricular level; *D* and *E*, in right ventricular cavity; and *F*, in inferior vena cava. Note that the greatest positivity of the intraventricular R wave is registered later than the corresponding deflection in Fig. 1. Time 0.20 and 0.04 second.

portions of the septum, which occurs in normal subjects and is not modified by the presence of right bundle branch block and which accounts for the inscription of the initial positive deflection of rsR complex in Lead V_1; and second, a later phase, corresponding to the activation of the septum below the lesion, which appears 0.04 to 0.05 second after the beginning of QRS and does not explain the first R in Lead V_1.

This new interpretation is supported by the following observations: In Fig. 1, the V_1 and right intraventricular leads are simultaneous. The peak of the intracavitary R wave follows the peak of the first R wave in Lead V_1. In the intraventricular tracing in Fig. 2, the peak of the R wave is inscribed up to 0.085 second after the beginning of the ventricular complex whereas, in the same figure,

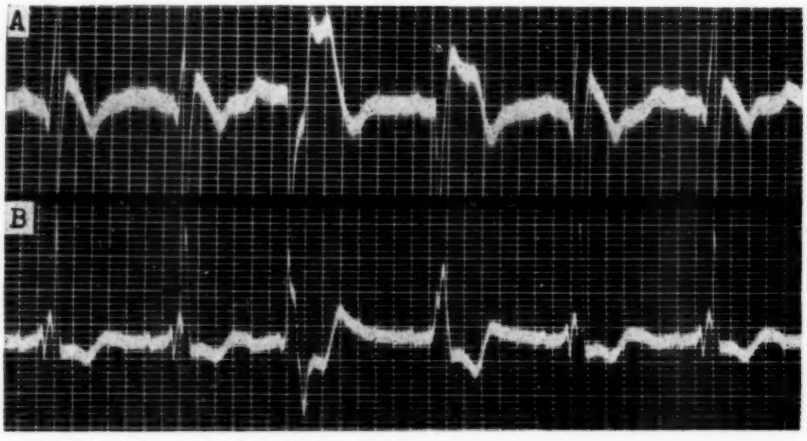

Fig. 3.—Right bundle branch block. The unipolar intracavity lead and precordial Lead V_1 were registered simultaneously. In *A*, the rapid intracavity complex is of the rsRS type with negative T wave. In *B*, the ventricular complex is of the rsR type. Time in 0.10 second.

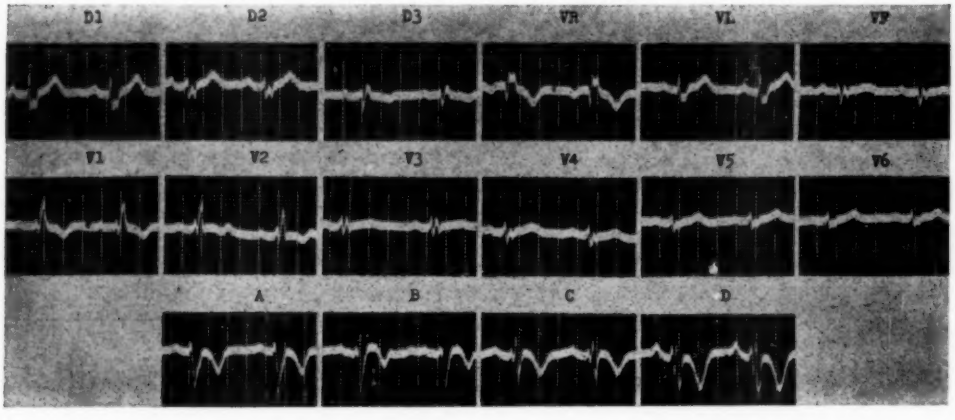

Fig. 4.—Right bundle branch block. Right intracavity tracings taken: *A*, near the pulmonary conus; *B* and *C*, at midlevel of the right ventricular cavity; and *D* in same cavity; near the tricuspid valve. Note that in *B*, *C*, and *D* the two positive deflections of the QRS complex are clearly visible. Time in 0.20 and 0.04 second.

the peak of the first positive deflection in V_1, V_2, and V_3 is inscribed at about 0.02-0.025 second after the beginning of the QRS complex. In the intraventricular tracings shown in Figs. 1 and 2, there is a deep notch in the ascending branch of R as though there were a tendency toward the inscription of two R

waves. This notch is also characteristic in tracings taken in dogs with right bundle branch block.[1] In the tracings shown, the peak of the notch is synchronous with the initial R in Lead V_1 (Figs. 1 and 2).

In a tracing made with the electrode in the right ventricular cavity, we were able to register a rapid complex of the rsRS type with a negative T wave (Fig. 3,*A*); we simultaneously registered the precordial Lead V_1, which was of the rsR type with a negative T and a marked notch in the ascending portion of the second positive deflection (Fig. 3,*B*). The first small positive deflection of the intraventricular tracing coincides with the initial R in Lead V_1; the waves in both tracings are synchronous and the late positive wave of the intraventricular tracing coincides in its first portion with the notch of the ascending branch of R′ in Lead V_1. It seems that in these intraventricular tracings we recorded the two phases of septal activation to which we have referred.

Fig. 4 shows an electrocardiogram of right bundle branch block. Tracings were registered in different portions of the right ventricular cavity. The electrocardiogram shown in *A* was taken with the electrode placed in the pulmonary conus; the ventricular complex is of the rS type with a negative T, and the positive deflection seems to correspond to the activation of the upper portion of the septum above the location of the branch block. A second positive wave is not registered, probably because the lead, quite high, is perpendicular to the forces which cause the activation of that portion of the septum situated under the lesion produced by the block. In *B* and *C*, the electrode was in at the mid-cavity portion of the ventricle; the ventricular complexes show two positive deflections which we believe represent the two phases of septal activation. The voltage of the second is higher, which leads one to believe that the electrode was placed nearer the apex than the auriculoventricular valves. In *D*, the electrode was at a higher level than in *B* and *C*, which explains why the two positive deflections are of similar magnitude. These variations in voltage in accordance with the position of the electrode support our point of view.

In Fig. 5 is shown another tracing of right bundle branch block. Strips *1* and *2* are unipolar tracings taken high in the auricle and in the mid-auricular region. In Strip *1* there is a ventricular complex of the qR type with negative T wave which is quite characteristic and similar to the complex we have described previously.[1] In Strip *2* there is a W type of ventricular complex which is not as characteristic. In Strips *3*, *4*, and *5* there are shown tracings taken at different levels in the ventricle. The tracings taken near the auriculoventricular valves show ventricular complexes of the qRS type (or rsRS type) with a negative T wave; the large positive deflection seems to correspond to inferior septal activation, located under the block. In the tracings taken at mid-ventricular level (Fig. 5, *4*) and at a lower ventricular level near the apex (Fig. 5, *5*), the positive deflection increases in voltage whereas the negative deflections diminish, this suggests that the lower portion of the septum is activated very much later than the upper portion. The time of appearance of the intrinsic deflection in the last electrocardiogram is 0.07 second after the beginning of the QRS complex.

In the same patient whose tracings are analyzed in Fig. 5, intracavity tracings were taken which show various peculiarities although the general configuration is quite similar. In Fig. 6, *C*, the exploring electrode was near the tricuspid valve. When the electrode was placed the second time, near the apex, we obtained the electrogram shown in Fig. 6,*A*, in which the second positive deflection is of greater voltage, very slurred, and its vertex recorded 0.08 second after the beginning of QRS. Most of the slurring observed in Lead V_1 of this figure is synchronous with the slurring of the second positive deflection of the lower intraventricular tracing. In this case, it does not seem that the slurring was

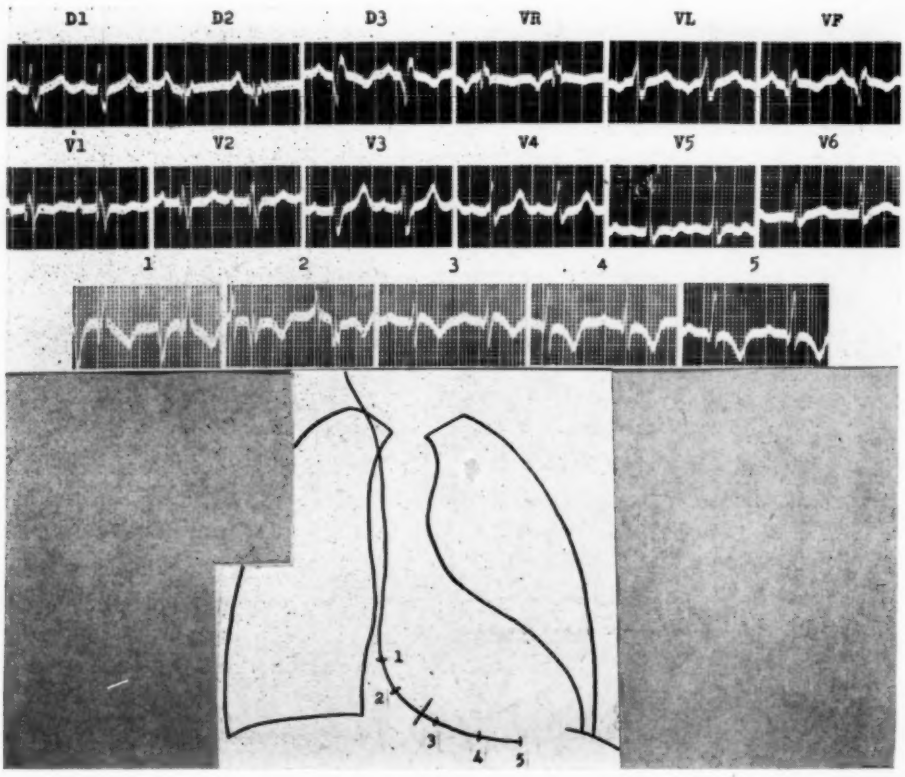

Fig. 5.—Right bundle branch block. Unipolar intracavity leads taken *1*, at high auricular level; *2*, at midauricular level; and *3*, *4*, and *5*, different levels in the right ventricular cavity according to the adjoining figure. The line marked between *2* and *3* corresponds to the approximate site of the tricuspid valve. Time in 0.20 and 0.04 second.

caused by the activation of the free wall of the right ventricle. A precordial lead taken a little above the C_1 precordial position (Fig. 6,*B*) shows a third positive deflection which does not appear in Lead V_1. This deflection is synchronous with the S′ wave of the intraventricular tracing, which makes us believe it is caused by the activation of the free wall of the right ventricle. This positive deflection is written rapidly with very slight slurring.

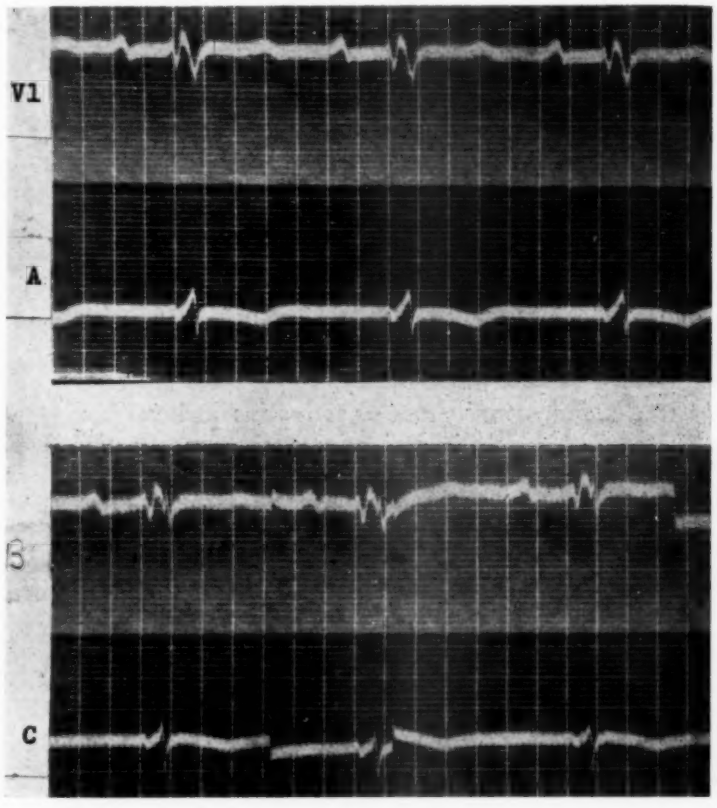

Fig. 6.—Right bundle branch block. Upper figure: the tracing shown in *A*, taken at a low level in the right ventricular cavity near the apex, is simultaneous with Lead V_1.

Lower figure: the tracing shown in *C*, taken at a high ventricular level, is simultaneous with a unipolar lead, *B*. The exploring electrode was located a little above precordial Position 1. Time in 0.10 second.

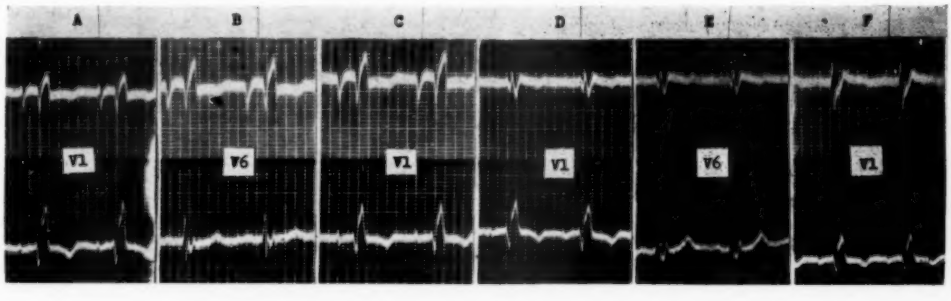

Fig. 7.—Right bundle branch block. The upper intracavity tracings registered simultaneously with Leads V_1 or V_6 (lower tracings) were taken: *A*, at midauricular level; *B* and *C*, at high auricular level; *D* and *E*, in ventricular cavity; and *F*, in inferior vena cava. Time in 0.10 second.

Fig. 7 is another electrocardiogram of right bundle branch block. The tracings, taken at a high auricular level (Fig. *7*, *A*, *B*, and *C*), show ventricular complexes of the rSR′ type with negative T waves, and are quite characteristic. Their general configuration is similar to that seen in Lead V_1; however, the R′ is more slurred in the intra-auricular tracing. The intraventricular tracings are of the rsR′S′ type with negative T waves. The second positive deflection is synchronous with the first portion of the ascending branch of the R′ in Lead V_1; there is hardly any slurring in the ascending portion. The final portion of the ascending branch of R′ of Lead V_1 is very slurred and follows the first unslurred portion of the same ascending branch in a broken line. We attribute it to the activation of the free wall of the right ventricle and it is synchronous with the S′ wave of the intraventricular tracing. The R wave in Lead V_6 is synchronous with the S wave of the intraventricular tracing and with the S wave in Lead V_1. In this case it is possible to determine four types of activation in Lead V_1: (1) the initial positivity which corresponds to the activation of the upper portion of the septum; (2) the initial negativity which is synchronous with R of Lead V_6 and can be referred to the activation of the free wall of the left ventricle; (3) the initial portion of the ascending branch of R′ which is not slurred and corresponds to the activation of the lower portion of the septum below the location of the block; and (4) the upper portion of R′ which is very slurred and corresponds to the activation of the free wall of the right ventricle.

The septal activation produced under the block in right precordial leads does not always manifest itself in the same way. In one tracing (Fig. 1) the second peak of the R wave in the intracavity lead is synchronous with the S wave of Lead V_1. In another (Fig. 2), the intracavity R is inscribed quite a bit later than the negative deflection of V_1 and corresponds in time to the final part of R′ in this lead. We have already stated that in the tracing of Fig. 3 the late positive deflection of the intraventricular tracing coincides, in its first portion, with the notch of the ascending branch of R′ in Lead V_1. We have also mentioned the fact that in some tracings (Fig. 7) the ascending branch of R′ in V_1 is a shaded line, the first portion of which is synchronous with the second positive deflection of the intracavity potential.

The findings which have been discussed show, that at times, it is possible to recognize in the right precordial leads the septal activation produced under the site of the block. One must not forget, however, that the time of the aforesaid activation is variable and depends, among other factors, on the thickness of the septum and on the existence of myocardial alterations in the septum.

In the electrocardiograms of the patient (Fig. 1), the R′ wave of the intracavity lead (second peak) was synchronous with the S wave of Lead V_1, which would suggest that it had a septal origin; for this to be possible, the right ventricular surface of the septum should be oriented in a special way, either by incurvation of the septum or by a strong clockwise rotation of the heart. However, in the tracings of other patients (Figs. 2, 3, 4, 5, 6, and 7), the R wave of the intracavity lead when there is only one positive wave or the R′ of the same tracing when there are two positive deflections are recorded considerably later than the S

wave of Lead V_1. The latter wave also has been attributed to the activation of the free wall of the left ventricle, especially the upper, posterior portions of the left ventricle which are situated diametrically opposite to the portion of the right precordium from which the potentials recorded in V_1 arise. In some tracings the peak of the negative wave in Lead V_1 is inscribed at the same time as the beginning of the intrinsic deflection in Leads V_5 and V_6 (Fig. 7). In other tracings, however, these deflections are not synchronous. In any case, the activation which seems to have most influence upon the production and the voltage of the S wave in Lead V_1 is the activation of the free wall of the left ventricle.

The R′ deflection in Lead V_1 is of greater amplitude than the initial positive deflection of the same lead. It is slurred and its duration at times reaches 0.08 or 0.09 second (Figs. 2 and 7). This positivity, when sustained for a rather long period, determines the slurring to which we have called attention. The S waves in Leads I, V_L, V_5, and V_6 and the major positive deflection in Lead V_R are also slurred. It appears that all these slurrings have a common cause. It is possible that activations arising in varied places may bring about or have an additive effect on their production. Thus, the septal activation may be retarded sufficiently so that it coincides in time with R′ in Lead V_1; this is what we see in Fig. 2. The R′ of the intraventricular tracing of Fig. 6, which corresponds to the activation of the lower portion of the septum, is very slurred and in the same case the deflection we have attributed to the activation of the free wall of the right ventricle shows slight slurring. The invasion of the free wall of the right ventricle by the process of activation possibly contributes to this slurring since it rapidly diminishes when the intrinsic deflection in Lead V_1 is recorded. In the tracing of Fig. 7, the slurring seems to originate in the free wall of the right ventricle.

We shall not stop to discuss the deflections occurring in Leads V_5 and V_6. It is sufficient to note that when there is an initial negative wave it is synchronous with the small R of Lead V_1. We have already pointed out the relations existing between the positive deflection in Leads V_5 and V_6 and the S wave in Lead V_1.

The wide and slurred S wave of the left precordial leads coincides with the R′ of the right precordial leads (Fig. 7).

Tracing Taken in the Cavity of the Left Ventricle of a Patient With Right Bundle Branch Block.—In a patient with coarctation of the aorta and a probably congenital right bundle branch block the presence of block led us to suspect the existence of an interauricular septal defect; angiocardiographic studies also strongly suggested the existence of such a septal defect. Upon studying the intracavity potential, we registered the potential of the right auricle at a high level (Fig. 8,*A*) which is quite characteristic in so far as the late R wave is concerned. The exploring electrode could not be directed toward the right ventricular cavity, due to the fact that it had passed through the septal defect and reached the left ventricular cavity. The tracing recorded in this cavity (Fig. 8,*B*) showed a purely negative (QS), slurred initial deflection with positive RS-T segment and T wave. The tracing is quite similar to tracings we have registered in the left ventricle of animals in which we have severed the right bundle branch.[1] From

this we inferred that the septal defect was an extensive one, notwithstanding the fact that there was an absence of abnormal acoustic phenomena over the precordium. Several months later, the patient succumbed and at necropsy we were able to detect a septal defect some 3.5 cm. in diameter.

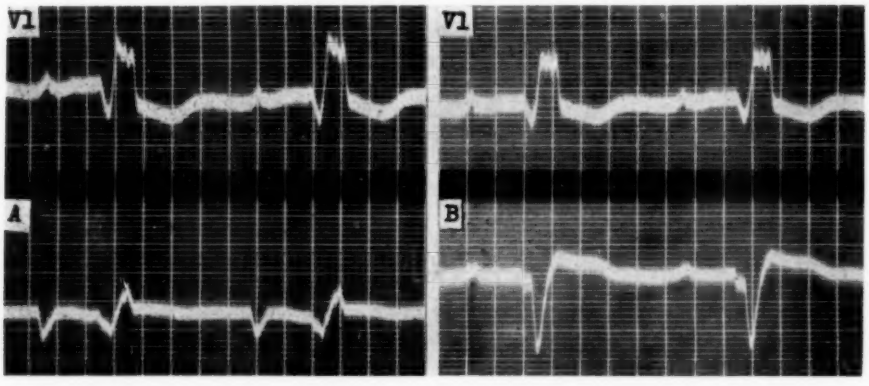

Fig. 8.—Right bundle branch block. Unipolar intraventricular tracings (lower portion of the figure) recorded simultaneously with Lead V_1 in a patient with interatrial septal defect. *A*, taken in the right auricle; and *B*, in the left ventricle.

COMMENT

The theory advanced concerning the possible existence of two phases in the activation of the interventricular septum in cases of right bundle branch block starts from the premise that in normal cases the first portion of the interventricular septum, and possibly of the heart, to be depolarized is the upper portion of the left ventricular septum. We have already stated that this is the opinion of Lewis. In support of this point of view, Mahaim[3] has described connecting rami that unite the common trunk or one and sometimes both branches of the bundle of His to the myocardium of the upper portions of the septum. These connections are more common in the left and superior portions of the septum and unite the origin of the left branch to the upper part of the interventricular septum. Mahaim believes that they should be regarded as an accessory form of conduction to which he has given the name paraspecific conduction. In the published paper,[3] which includes a discussion between Dr. Mahaim and Dr. F. N. Wilson on cardiac activation, the author states that the portion of the heart which first experiences depolarization, according to Wilson, is also the area in which he has demonstrated the accessory conduction system.

The interventricular septum is activated from left to right. In right intraventricular tracings of normal hearts, that activation produces an initial positive deflection. The Q wave in Leads V_5 and V_6 may be explained by the same activation. This is of short duration and because of it, the intrinsic deflection in the intracavity tracings appears 0.01 to 0.02 second after the beginning of the ventricular complex.

Since interventricular activation proceeds from left to right, there is no reason to believe that right bundle branch block alters the early activation of the septum. Conversely, left bundle branch block prevents left to right activation of the septum; consequently, the initial positive wave in the intraventricular tracings and the Q wave in Leads V_5 and V_6 are not inscribed. However, if the left bundle branch is not blocked high in the septum, left to right activation can persist. This would explain the small positive deflection in the right ventricle, recorded by Hecht in a case of left bundle branch block. We have obtained the same recording in only one case.

These views are supported by the fact that the vectocardiogram in right bundle branch block is similar in its first portion to that of normal tracings. This also suggests that right bundle branch block does not change the early activation.

Further investigation is necessary to determine if the right aspect of the septum beneath the block is activated at once or progressively from above downward.

In right precordial leads it is possible to recognize four different phases of activation: (1) The initial R corresponds to the depolarization of the superior portion of the septum. (2) The S wave represents the vectorial forces of the activation of the free wall of the left ventricle. (3) The ascending branch of R′ corresponds to the depolarization of the septum under the block. (4) The superior and final portion of R′ represents the activation of the free wall of the right ventricle.

Perhaps with future investigation it will be possible to determine hypertrophy of the septum, which until now has not been possible.

SUMMARY

1. It is quite probable that in the hearts of normal subjects the upper portion of the interventricular septum is early activated from left to right. In this way it is easy to explain the initial positive deflection of the normal right intraventricular tracing. This deflection has a higher voltage when the exploring electrode is closer to the upper portions of the septum.[2]

2. There is no reason to believe that right bundle branch block alters the early activation of the upper portion of the septum. Therefore, one must suspect two different phases in the activation of the interventricular septum in right bundle branch block: the first is an early phase which corresponds to the activation of the upper portions of the septum. The electrocardiographic findings during this phase are the same as those found in normal subjects and are not modified by the presence of the block. Such as early phase of septal activation could explain the inscription of the initial positive deflection of the rsR complex in Lead V_1. The second is a later phase which appears 0.04 to 0.05 second after the beginning of QRS and which is not related to the first R in Lead V_1. During this later phase, activation of the septum below the lesion takes place.

3. In cases of right bundle branch block we were able to register a rapid complex of the rsRS type with a negative T in leads taken from within the right ventricular cavity. The first small positive deflection of the intraventricular

tracing coincides with the initial R in Lead V_1. The late positive deflection of the intraventricular tracing coincides with the first portion of the ascending branch of R′ in Lead V_1. It appears that in these intraventricular tracings we recorded the two phases of septal activation.

4. It is possible to recognize in the right precordial leads the two phases of septal activation produced above and below the site of the block. One must not forget that the time of such activations is variable and depends, among other factors, on the thickness of the septum and on the existence of myocardial alterations in this septum.

5. In a patient with coarctation of the aorta and a probable congenital right bundle branch block, we were able to study the left intraventricular potential. The exploring electrode passed through an interauricular communication and reached the left ventricular cavity. The tracing was similar to those which we have registered in the left ventricle of dogs in which the right bundle branch was severed.

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THE EFFECT OF DICUMAROL ON THE HEART IN EXPERIMENTAL ACUTE CORONARY OCCLUSION

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THE increasing use of Dicumarol to prevent thromboembolic phenomena and propagation of the thrombus following coronary thrombosis[1-3] suggested the desirability of learning whether adverse myocardial changes might result from this therapy. It seemed possible, for instance, that the miliary myocardial hemorrhages commonly seen within infarcted areas could, under Dicumarol, result in progressive hemorrhagic extravasations or that other untoward effects might offset some of the possibly favorable effects of this drug.

The experimental approach to this problem was considered to offer the following advantages: (1) The site of occlusion can be chosen, and, therefore, a more uniform situation is offered for comparative studies. (2) The mechanism and rate of occlusion under experimental conditions are more uniform. (3) The effect of the drug on the myocardium can be studied accurately by sacrificing the animal and examining the heart at stated intervals following occlusion and administration of anticoagulants. (4) The uncertain effects of various drugs and methods of treatment invoked in patients with myocardial infarction do not complicate the experimental situation.

PROCEDURE

In thirty-two dogs, after administration of 1 to 2 mg. of morphine per kilogram of body weight subcutaneously and under intratracheal ether anesthesia, the heart was exposed through a lateral intercostal incision, and the pericardium was opened. In thirty-one animals, the left anterior descending artery, or in one instance a major branch, was freed from its bed. A ligature was then passed beneath the artery and tied. The pericardial incision was sutured, the lungs inflated, and the skin wound closed. Penicillin was administered to all animals in dosage of 50,000 units once or twice daily after operation for several days to

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control infection. On the day of operation and at least daily thereafter, rectal temperature, pulse rate, and clinical status were noted in all animals. In addition, prothrombin time, clotting time,[4] hematocrit, and sedimentation rate[5] were determined daily in all animals given anticoagulants.

Fifteen dogs received no Dicumarol (Table I). In fourteen dogs, Dicumarol was administered immediately after operation (Table II). Three dogs (Dogs 17, 20, and 21) also received heparin, beginning several hours postoperatively until the action of Dicumarol became apparent. Two additional dogs started on Dicumarol (Dogs 30 and 31, Table III) died the day following coronary ligation. They are not included in either series because death occurred before the prothrombin levels were measured and because only one dose of Dicumarol had been given.

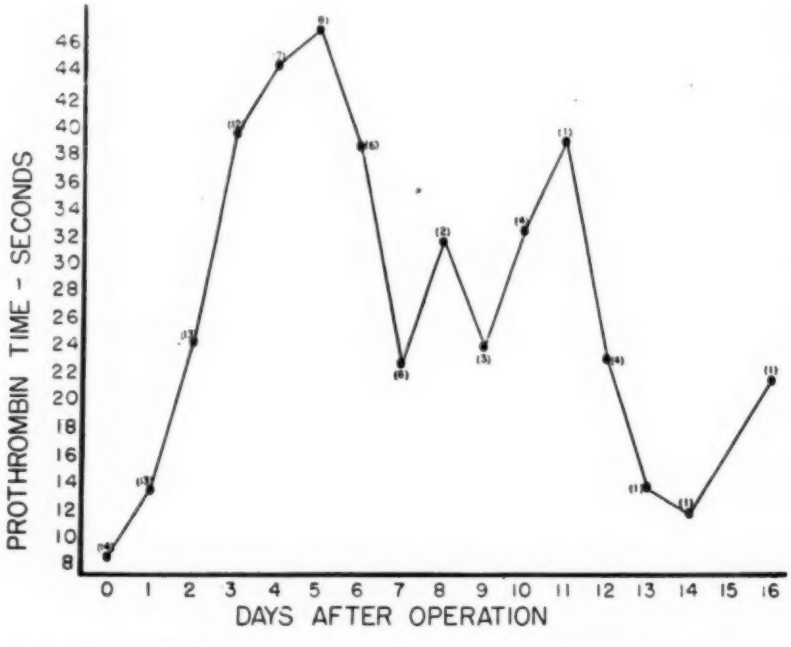

Fig. 1.—Average daily prothrombin times for all Dicumarol-treated dogs. Figures in parentheses indicate number of animals.

The aim of the Dicumarol therapy was to keep the prothrombin time between 20 and 30 seconds or 20 to 12 per cent of normal prothrombin activity in dogs. The average prothrombin time in normal dogs by the method used is 8.8 ± 1.1 seconds. The usual dosage schedule for Dicumarol (Table IV) was 50 mg. by mouth on the day of operation and 50 mg. on the first postoperative day. This generally produced a definite rise in prothrombin time by the end of the first postoperative day (Fig. 1) and a level of at least 20 seconds on the second day. Thereafter, the prothrombin time usually continued to rise for one or two more days, falling on the sixth or seventh day. In dogs permitted to survive for

TABLE I. CONTROL SERIES OF ANIMALS UNTREATED AFTER LIGATION OF THE LEFT ANTERIOR DESCENDING CORONARY ARTERY

CONTROLS												
EXP. DOG NO.	SURVIVAL TIME (DAYS)	POINT OF LAD LIGATION	ANASTOMOSIS IN LAD	INFARCT		HEMORRHAGE			HEART WEIGHT (GRAMS)	AREA GROSS EPICARDIAL SURFACE (CM^2)	AREA DIVIDED BY WEIGHT	REMARKS
				GROSS	MICRO	GROSS SURFACE	MICRO SURFACE	MICRO MURAL				
1	2 min.	high	0	0	0	0	0	0	88	0	0	Ventricular fibrillation during operation
2	40 min.	mid	0	0	0	0	0	0	107.5	0	0	Died spontaneously shortly after operation: microscopic congestion of small vessels in area of infarct
3	38 min.	mid	0	0	0	0	0	0	100	0	0	Died spontaneously shortly after operation
4	1	mid	0	++	++	0	0	+	78	11.2	.14	
5	2	mid	0	++	++	+++	++	++	92.5	12.7	.14	
6	3	mid	+	++	++	0	0	±	102	18.0	.18	Thrombosis of small vessels in area of infarction
7	3	mid	+	++	++	++	++	+	112	9.5	.08	Thrombus 2.0 m.m. long in LAD proximal to tie
8	5	high	+	+++	+++	+++	+++	+++	126.5	12.2	.10	Thrombosis of small vessel in area of infarction
9	6	mid	+++	0	0	0	0	0	70.5	0	0	
10	7	high	+++	+++	+++	++	0	0	98.5	16.0	.16	
11	7	mid	+++	++	+	+	+	+	73.4	0	.0	
12	7	mid	+++	++	++	+	0	0	62	11	.18	
13	7	mid	+	+	±	0	0	0	91	14.2	.16	
14	12	mid	+	++	++	+	±	+	72	7.4	.10	
15	14	mid	++	++	++	0	0	±	84	7.0	.08	
								Sum Dogs 4 to 15		119.0	1.32	
								Average		9.9	0.11	

0 = absent
± = minimal
+ = slight
++ = moderate
+++ = marked
LAD = left anterior descending coronary artery

TABLE II. SERIES OF ANIMALS TREATED WITH ANTICOAGULANTS FOLLOWING CORONARY ARTERIAL LIGATION

DICUMAROL												
EXP. NO.	SURVIVAL TIME (DAYS)	POINT OF LAD LIGATION	ANASTOMOSIS IN LAD	INFARCT		HEMORRHAGE			HEART WEIGHT (GRAMS)	AREA GROSS EPICARDIAL INFARCT (CM^2)	AREA DIVIDED BY WEIGHT	REMARKS
				GROSS	MICRO	GROSS SURFACE	MICRO SURFACE	MICRO MURAL				
16	2	high	0	+++	+++	++	+	+	103	24.7	.24	
17*	2	mid	+	++	++	+	0	+	82.5	6.5	.08	Slight hemothorax; hemorrhage in operative wound and site of venipunctures
18	3	high	+	+++	+++	+	+	+	93	18.0	.19	
19	4	low	0	+	0	0	0	0	60.5	9.5	.16	Hemothorax (150 c.c.), atelectasis and anterior mediastinal hemorrhage; died spontaneously
20*	4	mid	++	+	+	0	0	+	71	2.3	.03	
21*	4	mid	0	++	++	++	+	++	111	14.0	.13	Hemothorax (125 c.c.); hemorrhage into operative wound; thrombosis of small vessel in area of infarction
22	5	mid	0	++	++	++	+	++	77.8	6.8	.09	External, subcutaneous, and mediastinal hemorrhage at operative site; hematocrit 20 per cent
23	6	mid	+++	++	++	++	X	+++	62	8.5	.14	Hemothorax (475 c.c.); hemorrhage in operative wound and site of venipunctures; thrombosis of small vessel in area of infarct
24	6	Branch	+	+	+	0	0	0	81.4	2.5	.03	Hemothorax (850 c.c.) and shock; hematocrit 14 per cent; died spontaneously
25	7	low	++	±	0	0	0	0	71	0.9	.12	
26	7	mid	++	++	++	++	++	+++	70	2.5	.04	Thrombosis of small vessel in area of infarct
27	12	mid	+++	+	+	0	0	0	88	0	0	
28	12	low	+	+	+	0	0	+	104	0	0	
29	14	mid	+++	++	++	+	0	+	72	5.4	.08	
									Sum	101.6	1.33	
									Average	7.3	.10	

0 = absent ± = minimal + = slight ++ = moderate +++ = marked LAD = left anterior descending coronary artery

X = no observation made

* = Heparin given immediately after operation until therapeutic prothrombin level was reached.

therapeutic prothrombin level was reached.

TABLE III. OPERATED ANIMALS TREATED WITH DICUMAROL NOT INCLUDED IN TABLE II

EXP. DOG NO.	SURVIVAL TIME	POINT OF LIGATION LAD	ANASTOMOSIS IN LAD	INFARCT		HEMORRHAGE			HEART WEIGHT (GRAMS)	AREA GROSS EPICARDIAL INFARCT (CM^2)	AREA DIVIDED BY WEIGHT
				GROSS	MICRO	GROSS SURFACE	MICRO SURFACE	MICRO MURAL			
30	23 hours	mid	+	+	±	0	0	0	79	7.0	.10
31	22 hours	high	0	+	0	0	0	0	96	14.2	.15
32	16 days	none	0	0	0	0	0	0	113	0	0

0 = absent
+ = slight
± = minimal
LAD = left anterior descending coronary artery.

TABLE IV. PROTHROMBIN TIMES AND DICUMAROL DOSAGE FOR ALL TREATED ANIMALS

DOG NO.	DAYS	OPERATION																PROTHROMBIN TIME (AFTER FIRST P. O. DAY)			TOTAL DICUMAROL
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	AV.	MIN.	MAX.	DOSAGE MG.
16	6.5*	10.9*	20.6															20.6	20.6	20.6	100
	H	H																			HEP 80 mg.
17	8.3*	11.3*	21.7															21.7	21.7	21.7	100
18	—	15.1*	25.9															25.9	25.9	25.9	100
19	6.9*	15.4*	33.4	67.2														50.3	33.4	67.2	100
	H	H																			HEP 90 mg.
20	7.5*	15.5*	26.2	46.7														36.5	26.2	46.7	100
	H	H																			HEP 90 mg.
21	8.0*	11.6*	20.3	31.0	37.2													29.5	20.3	37.2	100
22	—*	***	—	24.3*	37.1	61.0	132.0											63.6	24.3	132.0	250
23	—	10.5*	—	22.4	14.2*	21.8	58.6											29.3	14.2	58.6	100
24	8.8	18.1	34.5	78.0	78.8	—	51.3											60.7	34.5	78.8	100
25	7.4	13.5	25.9	38.1	51.7	35.6	—	17.0										33.7	17.0	51.7	100
						(*)															
26	6.8*	11.0*	18.6	25.5	28.8	26.6	—	28.3										25.6	18.6	28.8	125
27	9.7*	12.3*	27.6	41.0	—	41.1	26.6	10.8*	—	37.0	35.5	—	12.3					29.0	10.8	41.1	150
28	9.0*	11.6*	20.0	31.9	—	37.9	37.6	23.8	—	9.8*	8.8	—	23.6					24.6	8.8	37.9	150
29	9.1*	16.6*	—	35.0	40.5	42.5	29.4	19.3*	28.2	—	51.5	39.1	32.3					35.3	19.3	51.5	150
30	9.7*																	—	—	—	50
31	9.1*																	—	—	—	50
32	8.8	—*	13.0	20.4	—	40.4	28.5*	33.1	35.1	24.3*	34.1	—	23.7	13.6	11.7*	—	21.5	25.0	11.7	40.4	250
Av.	8.3	13.3	24.0	39.5	44.6	47.2	38.7	22.6	31.7	23.7	32.5	39.1	23.0	13.6	11.7	—	21.5	34.4	20.5	49.3	122 mg.

*Each asterisk represents 50 mg. dicumarol.
(*) equals 25 mg. dicumarol.

H. Doses of heparin given on days designated.
HEP. Total amount of heparin received.

more than seven days, additional doses of Dicumarol (25 or 50 mg.) were required to maintain an elevated prothrombin time (Table IV).

One animal (Dog 32, Table III) was subjected to the routine operation of exposing the heart and opening the pericardium, but the coronary artery was not ligated; this dog was treated effectively with Dicumarol for sixteen days (Table IV) and then sacrificed. At post-mortem examination, a localized healed pericarditis was present; interarterial coronary anastomoses, myocardial infarction, and hemorrhagic manifestations were absent.

The animals were sacrificed at various intervals after operation. The hearts were injected according to the method of Schlesinger,[6] and the following gross pathologic examinations were carried out: The size and character of the infarcts and the rate and extent of development of anastomoses between the coronary arteries were studied; the degree and extent of macroscopic hemorrhage were estimated. Numerous microscopic studies were made on representative sections derived from serial blocks of tissue removed from the heart. These included observations on the extent, homogeneity, and character of the myocardial infarction and necrosis, the presence or absence of thrombi within the small vessels in and near the infarcted area, the presence of microscopic hemorrhage, and the characteristics of the reparative process within the infarcted area. The pathologic gross and microscopic examinations of the heart were made without knowledge by the examiners whether or not Dicumarol had been administered.

Determinations of the size, degree and stage of development of hemorrhage, infarction, and repair were made by combined gross and microscopic observations after the injection of the coronary arteries with radiopaque mass. The heart was unrolled so that it lay flat in one plane, and a roentgenogram was taken. A tracing was made of this film. Detailed observations of the results of dissection and observation of the coronary arterial tree, and the pathologic changes in the myocardium were recorded on the tracing. The changes in color and consistency on both the epicardial and endocardial surfaces of the heart were carefully mapped in this way. The entire heart was then cut in slices by parallel transverse incisions one centimeter apart from apex to base. The cut surface of each slice of muscle was next placed on a glass plate and a tracing made of gross changes in the cross-sectional plane of the myocardium. Labelled, multiple blocks of tissue were then cut from these slices of myocardium to include representative sections of every part of the ventricles and particularly the areas of gross pathology including transitional zones. Microscopic slides prepared from these blocks were fixed in Zenker's solution, cut, and stained with hematoxylin and eosin. In all, 378 slides were prepared from the thirty-two hearts studied. Gross and microscopic changes were correlated, and the character, degree, and extent of various pathologic processes of infarction, necrosis, hemorrhage, and repair were mapped.

Prothrombin Time Method.—Prothrombin times in the experimental animals were measured by the one-stage Quick method,[7] as modified by Schlesinger.[8] These modifications are described here in detail since they are not widely known,

and in our experience have contributed to the accuracy and facility of the procedure.

Preparation of Thromboplastin: Commercial Difco (rabbit brain) thromboplastin is used. One tube (0.15 Gm.) is emptied into a chemically clean test tube (14 by 100 mm.) and 2.5 c.c. normal saline are added. This mixture is incubated for fifteen minutes in a water bath (40 to 45° C.), stirred several times, and then centrifuged for five minutes. The supernatant fluid is removed and saved. Extraction is repeated twice more, with 2.5 c.c. saline used each time, the supernatant fluid being collected in separate tubes. The activity of each tube of supernatant fluid is tested in duplicate or triplicate against one or two normal subjects who are used repeatedly for this purpose and whose prothrombin times are known to remain constant. Supernatant fluids giving prothrombin times of 13 to 16 seconds are saved and mixed; those giving higher times are discarded. The prothrombin time for the mixed supernatant fluids is determined similarly. This thromboplastic reagent is pipetted (0.1 c.c.) into chemically clean serologic tubes (75 by 9 mm.) which are stoppered and kept frozen (−12°C.) until needed. Thromboplastic reagent prepared in this way has the great advantage of retaining its original activity for periods of at least seven months. The daily necessity of preparing fresh thromboplastin and checking it with normal controls is thereby obviated.

Technique of Prothrombin Time Determination: Blood is drawn by clean venipuncture into a dry syringe and exactly 4.5 c.c. are mixed in a chemically

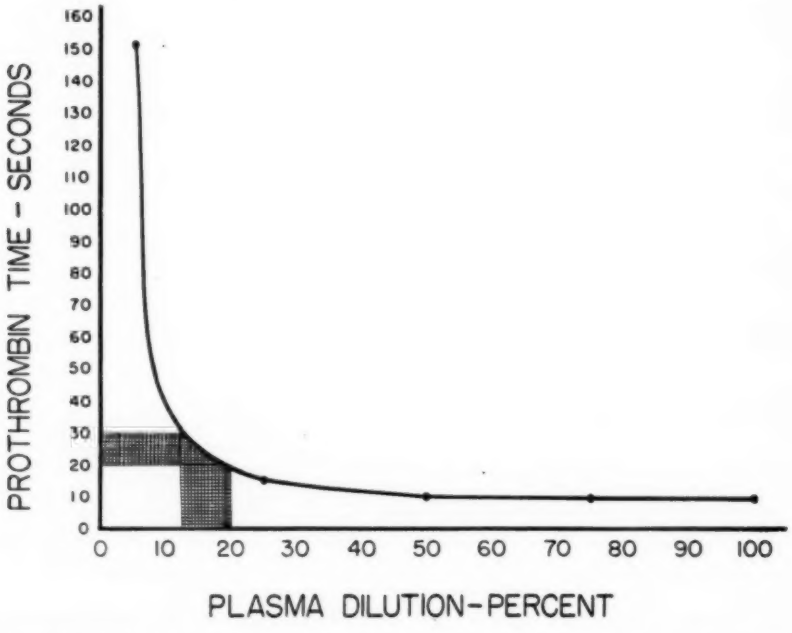

Fig. 2.—Prothrombin times for normal dog plasma diluted with 0.85 per cent saline. Crosshatched area indicates therapeutic range of 20 to 30 seconds prothrombin time, corresponding to plasma concentration of 20 to 12 per cent.

clean tube with 0.5 c.c. 0.1 molar sodium oxalate. The blood is centrifuged at 1,500 revolutions per minute for five minutes and the plasma removed. A serologic tube containing the 0.1 c.c. of the stored frozen thromboplastin extract is warmed in a water bath at 37.5° C. for ten minutes. One-tenth cubic centimeter of the plasma to be tested is added and the tube returned to the water bath for thirty to sixty seconds. Exactly 0.1 c.c. of 0.02 molar calcium chloride solution is drawn into a tuberculin syringe through a 25-gauge hypodermic needle from a small tube kept in the water bath. With one hand, the solution is ejected forcibly from the syringe into the thromboplastin-plasma mixture, and a stopwatch is started simultaneously with the other hand. A wooden or nichrome wire applicator is plunged rhythmically into the mixture and observed through the wall of the water bath to note the moment of adhesion of clot to applicator. When the first clot appears, the watch is stopped. All determinations are done in duplicate, and closely agreeing values are averaged.

Normal Values: Blood was obtained from the animals used in this study by clean femoral venipuncture and was placed in the refrigerator immediately. The prothrombin time was determined in duplicate thirty to one hundred twenty minutes thereafter. The prothrombin time of undiluted plasma for normal dogs was 8.8 ± 1.1 seconds. Values by this method for normal dog plasma in various dilutions with saline are shown in Fig. 2.

RESULTS

The results of fifteen experiments in which the dogs did not receive Dicumarol are summarized in Table I. The results of fourteen experiments in which the dogs were treated with Dicumarol are given in Table II. The survival times, the point of ligation, and the other details of the experimental procedure in the control and treated groups were kept closely similar.

The Development of Interarterial Coronary Anastomoses.—Gross anastomoses, sufficiently well-developed so that the arterial tree distal to the occlusion was well filled with injection mass, appeared six days or more after ligation (indicated by ++ and +++ in Tables I and II). Dicumarol had no apparent effect on the incidence, speed of development, or magnitude of such anastomoses. Five of seven dogs in the control series (Table I) and five of seven dogs in the Dicumarol series (Table II) sacrificed six days or more after ligation showed anastomoses of this type. In animals of both series sacrificed less than six days after ligation of the coronary artery, anastomoses of this type were usually absent or only incompletely developed (indicated by 0 and ± in Tables I and II).

Size and Characteristics of Infarction.—The size of the infarct was related closely to the location of the occlusion of the coronary artery and the minute variations in the geography of the coronary tree. The infarcts were located in the areas of myocardium supplied by the occluded vessels. Minor variations in the configuration of the branches distal to a ligated artery, and differences in the level of ligation which appeared insignificant at the time of operation produced considerable differences in the area of infarction. Dog 9 presented a

good example of this phenomenon. An unusually well-developed anastomosis was found, with complete filling of the left anterior descending artery distal to the occlusion; there was no evidence of myocardial damage on gross and microscopic study.

The infarcted areas were of similar extent on the epicardial surface and intramural layer. The endocardial extent of infarction was often smaller, however, and quite irregular. In six instances (Dogs 11, 13, 19, 25, 30, and 31), the correlation between gross and microscopic extent of infarction was inexact. In each case, the gross estimation of the infarction was the more extensive and less reliable.

In spite of these difficulties, an attempt was made to measure the size of infarcts and compare the treated and untreated series in this way. The area of the epicardial extent of grossly observed infarction was measured with a planimeter on the tracing of the roentgenogram of every heart; the ratio of this area to the heart weight was also calculated (Tables I, II, and III). The range of these figures from 0 to 24.7 cm.^{2} area and a 0 to 0.24 ratio emphasizes the importance of the variable factors which have been described. Quantitative comparisons between the control and treated series of the areas of infarction subsequent to ligation at similar levels show no significant differences; if anything, the averages for the treated series are smaller than those of comparable untreated groups, indicating a possible beneficial effect of Dicumarol, and certainly no harmful effect. The distance of the border of infarction from the nearest well-injected vascular twigs derived from unoccluded vessels was also the same in the two groups of hearts.

An attempt also was made to measure the size of the transition zone between infarcted and normal muscle, since, theroretically, anticoagulant therapy might influence processes particularly in this critical zone. The marked irregularity in distribution and the interdigitation of normal and infarcted muscle, as well as the great variation in inflammatory reaction in this zone, defied quantitative analysis. No qualitative difference in the morphologic characteristics of the infarcts and their zones of transition was demonstrated between the control and Dicumarol groups upon gross and microscopic study.

Hemorrhage in Infarction.—The occurrence of surface hemorrhage in the area of infarction was inconstant in all animals sacrificed less than two or more than seven days after coronary arterial ligation (Tables I and II). Although marked congestion of the capillaries may be seen in the involved myocardium within an hour after coronary ligation (Dog 2), gross hemorrhagic extravasation in the myocardium appeared only after a day or more following ligation; after seven to twelve days there was progressive absorption and disappearance of hemorrhage. It was decided, therefore, to compare the extent of hemorrhage in treated and untreated dogs that survived two to seven days after coronary ligation. Grossly visible hemorrhage was apparent in the area of infarction on the epicardial or endocardial surfaces in six of nine dogs in the control series and in seven of eleven dogs in the Dicumarol series that survived two to seven days. These surface hemorrhages were extensive in four of the control dogs and five

of dogs which received Dicumarol. The extent of surface hemorrhage varied considerably from heart to heart without evident relation to the administration of Dicumarol.

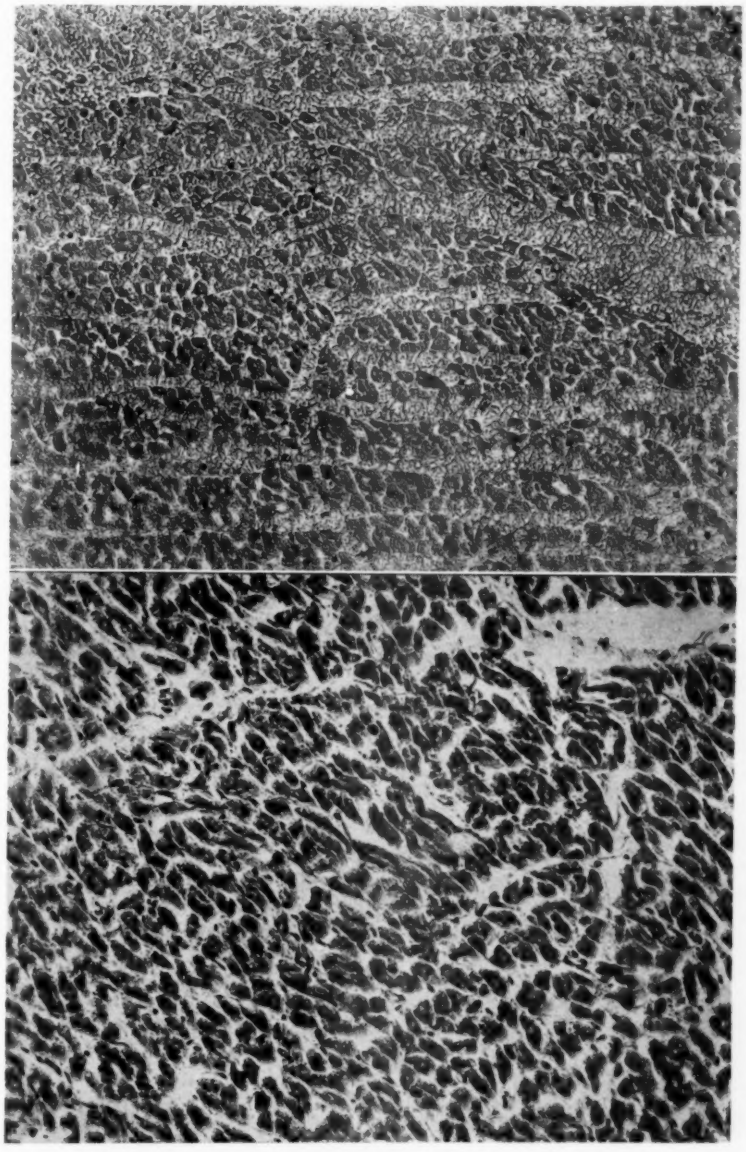

Fig. 3.—Intramural hemorrhage in infarcted muscle (*A*) compared with normal Myocardium; (*B*) in untreated Dog 8. Hematoxylin and eosin stain, ×200.

Microscopic examination confirmed the observation of gross epicardial and endocardial hemorrhage, and in several instances in both series, disclosed extensive hemorrhagic extravasation in the depths of the muscle among the myo-

cardial fibers. Fig. 3, for example, shows intramural hemorrhage into the infarcted muscle in a control animal (Dog 8) compared with normal myocardium from an uninvolved area in the same animal. There was no apparent difference in the results of microscopic examination in the two groups.

Arterial Thrombosis.—Thrombi were seen in small vessels within the infarcted areas in two dogs of the control series and three of the dogs treated with Dicumarol. Fig. 4 shows an arteriolar thrombus in the infarcted myocardium of a treated animal (Dog 23). A thrombus at the site of arterial ligation was observed in only one instance in the entire study; in a control animal sacrificed three days after ligation, a small thrombus about 2.0 mm. long was found firmly adherent to the vessel wall proximal to the tie. No definite effect of Dicumarol on the presence of thrombi was observed.

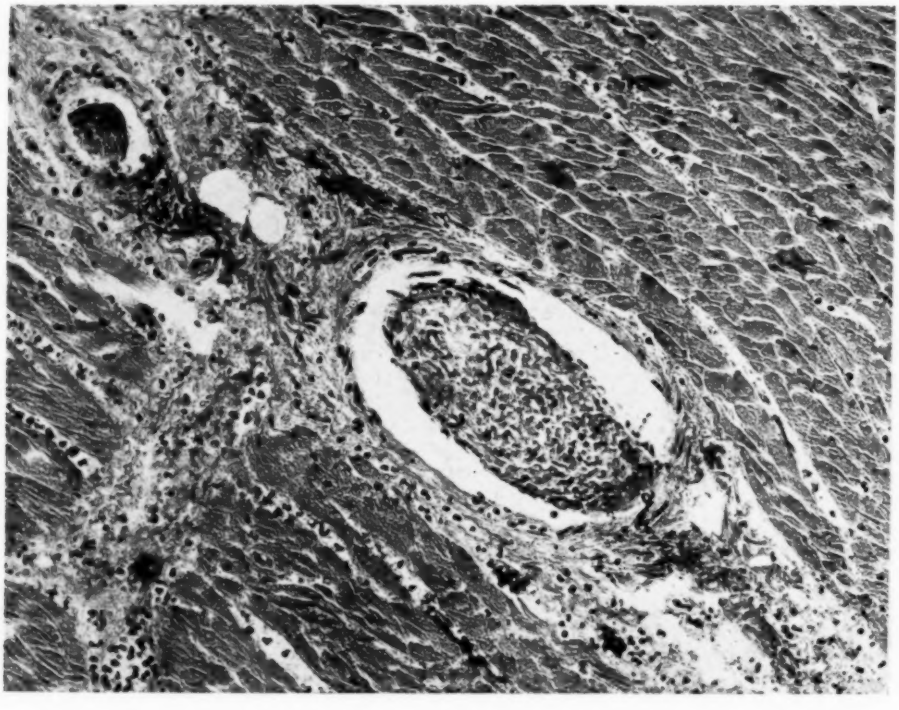

Fig. 4.—Arteriolar thrombosis in infarcted muscle in Dog 23 treated with Dicumarol. Hematoxylin and eosin stain, ×200.

Process of Repair.—No apparent difference between the Dicumarol-treated and control groups was noted in the process of healing or repair in the area of infarction. Microscopic slides from the five animals surviving twelve to fourteen days were studied by two separate observers without knowledge of the identity of the slides. Attempts were made to grade the character, age, and extent of the various aspects of the reparative process such as the removal of dead tissue,

the cellular response, and the deposition of collagen. No differences were found between the control and treated groups.

Effect of Heparin and Dicumarol.—Heparin was administered to three dogs in order to decrease blood coagulability during the interval until Dicumarol action became definite. No apparent differences were found in the hearts of these animals as compared with the group treated with Dicumarol alone or as compared with the control group (Tables I and II).

Effect of Marked Hypoprothrombinemia.—Four treated dogs (Dogs 19, 22, 23, and 24) had undue elevations of prothrombin time (Table IV). Two of these dogs died and the other two were sacrificed when in extremis. Their course was marked by a rapid rise in prothrombin time and blood clotting time, a lowered hematocrit, rise in pulse rate, and clinical manifestations of shock. It should be noted that while one of these animals received a total dose of 250 mg. of Dicumarol, the other three received only the usual dose of 100 milligrams. The extent of hemorrhage, size and healing of infarct, and anastomotic circulation in these animals were similar to the untreated control animal or animals receiving Dicumarol in which the prothrombin times were maintained at more normal clinical levels.

Extracardiac hemorrhage of moderate to marked extent was noted in six animals (Dogs 17, 19, 21, 22, 23, and 24) treated with Dicumarol; two of these were also treated with heparin (Dogs 17 and 21). Hemorrhages were present in the subcutaneous tissue at the site of needle punctures and also in the pleural cavities and the operative wound. The maximum prothrombin times in these six dogs varied from 21.7 to 132 seconds and averaged 66 seconds. In the eight dogs not showing extracardiac hemorrhage, the maximum prothrombin times varied from 20.6 to 51.7 seconds and averaged 34 seconds. Hemorrhagic manifestations generally were not observed when the prothrombin time was kept below 50 seconds except in the animals receiving both Dicumarol and heparin; in the latter group, hemorrhage occurred at considerably lower levels of prothrombin concentration.

COMMENT

This investigation was undertaken to obtain decisive evidence of the presence or absence of adverse myocardial effects which might be induced by Dicumarol. It is apparent that under the conditions of these studies, Dicumarol exerts no such harmful influence. It is theoretically possible that minor adverse or beneficial effects may be exerted which are not discernible in the presence of the wide individual variations of the anatomy of the coronary tree in dogs and variations of the extent of anastomosis, hemorrhage, and infarction after coronary ligation.

The size of the infarcts produced in both groups of animals was entirely comparable and was in accord with expectation on the basis of the artery occluded. Similarly, Dicumarol exerted no apparent effect on the healing or reparative process, which was closely studied in all hearts. Subepicardial and subendocardial hemorrhages were grossly and microscopically visible in the hearts

of animals receiving Dicumarol; the incidence and magnitude of the extravasations were the same, however, in the untreated control group. These results are particularly significant since the elevation in the prothrombin time in our dogs was generally twice that employed clinically, inasmuch as the normal prothrombin time of the dog is approximately one-half that of man. In many animals, moreover, undue elevations in prothrombin time occurred occasionally in the postoperative period, and reached levels of 59 to 132 seconds in four animals. No consequent increased myocardial extravasations were seen in these four animals grossly or microscopically, desipite the fact that they showed gross hemorrhage at post-mortem examination either subcutaneously or in the serous cavities.

Previous studies[9,10] have indicated that both clincially and experimentally produced anastomotic intercoronary communications protect the myocardium from some of the dire consequences of coronary occlusion. It was of interest, therefore, to observe the development of anastomotic channels, as disclosed by the method of Schlesinger[6] in both groups of hearts. The development of collateral anastomotic channels between the coronary arteries was the same in both groups; on or about the fourth day following occlusion, unmistakable evidences of collateral communications were observed between the left anterior descending artery distal to the tie and the left circumflex or other branches of the left descending coronary artery. The magnitude of these anastomotic vessels showed marked increase on and after the sixth day of survival.

The effect of Dicumarol on the development and extension of a thrombus in the left anterior descending artery, on the healing of such a thrombus, and the effect of Dicumarol in the prevention or retardation of mural thrombi were not studied. However, previous investigations have shown that anticoagulant therapy in the form of heparin will prevent the formation of coronary arterial and cardiac mural thrombi when sodium ricinoleate is injected or infiltrated into the coronary arteries or the myocardium.[11,12] Post-mortem observations in man regarding the effect of Dicumarol on naturally occurring coronary thrombi and mural thrombosis will undoubtedly clarify these questions; these aspects of the problem therefore, were not subjected to experimental investigation.

SUMMARY

1. In thirty-one dogs, the left anterior descending coronary artery or a major branch was ligated. The effect of the oral administration of Dicumarol on the myocardium and coronary arteries was studied in fourteen animals. In three dogs, heparin was administered several hours postoperatively until the effect of Dicumarol was apparent. Fifteen dogs served as a control group.

2. The incidence and magnitude of hemorrhagic extravasations on the endocardium and pericardium were the same in the treated and untreated groups.

3. The incidence and magnitude of miliary hemorrhages on microscopic examination of the heart muscle were similar in the dicumarolized and control animals.

4. In a small group of dogs in which sufficient Dicumarol was administered to elevate the prothrombin time to levels as high as 132 seconds, no increase in the hemorrhagic phenomena was observed in the myocardium.

5. The size of the infarcts in the Dicumarol-treated and untreated animals showed no significant differences. The size of the infarcts was that which could be anticipated on the basis of the artery occluded.

6. There were no apparent differences in the healing or reparative processes in the hearts of the Dicumarol-treated and the control animals.

7. Thrombotic occlusions of the smaller arteries were found within the infarcted area in dogs receiving Dicumarol approximately as often as in the untreated group. No thrombi were found in the region of the tie below the point of occlusion. In one instance, an untreated animal, a thrombus was found in the region of the tie above the point of occlusion.

8. No mural thrombi were found in the auricles or ventricles in the treated or in the untreated animals.

9. The development of collateral anastomotic channels between the coronary arteries was the same in both groups. On or about the fourth day, unmistakable evidences of collateral vessels between the left anterior descending branch distal to the tie and the circumflex branch of the left coronary artery were observed. On and after the sixth day of survival, the magnitude of these anastomotic vessels was markedly increased.

CONCLUSION

The results of this investigation reveal that Dicumarol produces no adverse effects on the myocardium of dogs which retard the healing process or the development of collateral circulation in experimentally produced myocardial infarction.

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INCOMPLETE DIVISION OF THE ATRIOVENTRICULAR CANAL WITH PATENT INTERATRIAL FORAMEN PRIMUM (PERSISTENT COMMON ATRIOVENTRICULAR OSTIUM)

Report of Five Cases and Review of the Literature

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IN THE field of congenital cardiac disease of human beings, the condition characterized by incomplete division of the atrioventricular canal is of interest both from clinical and developmental viewpoints. Furthermore, since the lesion is relatively uncommon, we consider it pertinent to report five cases in which the patients have been observed at the Mayo Clinic. In three cases, the degree of incomplete division was readily manifest. There was a common atrioventricular canal guarded by one valve. In the remaining two cases, while the once common atrioventricular canal had been divided into right and left halves, cardiac defects were present which forced one to interpret these cases as portraying a lesser degree of the anomaly seen in the complete form in the first three cases.

The condition which we are classifying as incomplete division of the atrioventricular canal with patent interatrial foramen primum has been given a variety of names by other authors. The most frequently employed designation is "persistent common atrioventricular ostium" or "ostium atrioventriculare commune." It has also been called "persistent ostium primum with cleft mitral valve" and "incomplete double heart." Some of the cases classified by Abbott[1] as cases of defects in the auricular septum below are examples of the condition herein reported.

REPORT OF CASES

Case 1.—A white boy, aged 5 months, was admitted to the hospital in extremis on May 20, 1939. For two days prior to his admission, the child had suffered from a coryza and fever. Mongolian features were obvious. Cyanosis was marked. Pulmonary râles were present anteriorly and posteriorly and obscured the heart sounds. This made it impossible to tell whether or not a murmur was present. The cardiac rate was 120 beats per minute. Oxygen therapy was promptly started, but the infant died two hours after his admission to the hospital.

At necropsy the heart was globular in shape; it was enlarged and weighed 50 grams. (The estimated weight of a normal heart of a boy of this age is 23 grams.) When the heart was

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opened, the region of major interest was found at the junction of the atria and ventricles. Defects were observed in the valvular structure, the interatrial septum, and the posterior portion of the interventricular septum. Instead of two atrioventricular ostia, each guarded by its own valve as in normal hearts, there was but one atrioventricular ostium which was common to both sides of the heart. This ostium was associated with one large atrioventricular valve. When viewed from above, it was evident that the single atrioventricular valve was composed of one large anterior cusp, a somewhat smaller posterior cusp, a left lateral cusp, and two smaller right lateral cusps (Fig. 1). When the heart was examined in the conventional manner, it was observed that the anterior and posterior tricuspid cusps were normally placed and attached. They corresponded to the two small right lateral cusps of the common atrioventricular valve. The septal cusp of the tricuspid valve was abnormal. It was cleft and consisted of anterior and posterior components (Fig. 2,*a*). The anterior half of the septal tricuspid cusp represented the right half of the large anterior cusp of the common atrioventricular valve, and the posterior half of the septal tricuspid cusp represented the right half of the posterior cusp of the common atrioventricular valve.

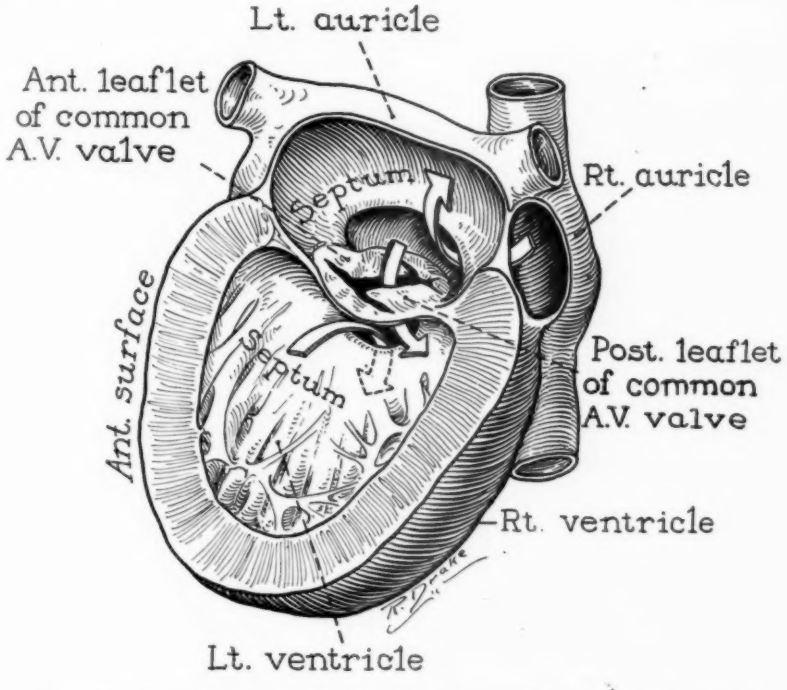

Fig. 1.—Sketch of heart in Case 1. The lateral walls of the left atrium and ventricle have been removed. The atrioventricular canal is common to both sides of the heart. It is guarded by a single valve possessing large anterior and posterior cusps and two right lateral cusps and a left lateral one. The interatrial foramen primum is patent as is the posterior upper portion of the interventricular septum.

Similar conditions were observed when the interior of the heart was viewed from the left. The posterior cusp of the mitral valve was properly placed and developed. It represented the small left lateral cusp of the common atrioventricular valve. The anterior or aortic cusp of the mitral valve was essentially similar to the septal tricuspid cusp. It also was cleft (Fig. 2,*b*). The anterior half of this cusp represented the left half of the anterior cusp of the common atrioventricular valve, and the posterior half of the aortic mitral cusp represented the left half of the posterior leaflet of the common atrioventricular valve.

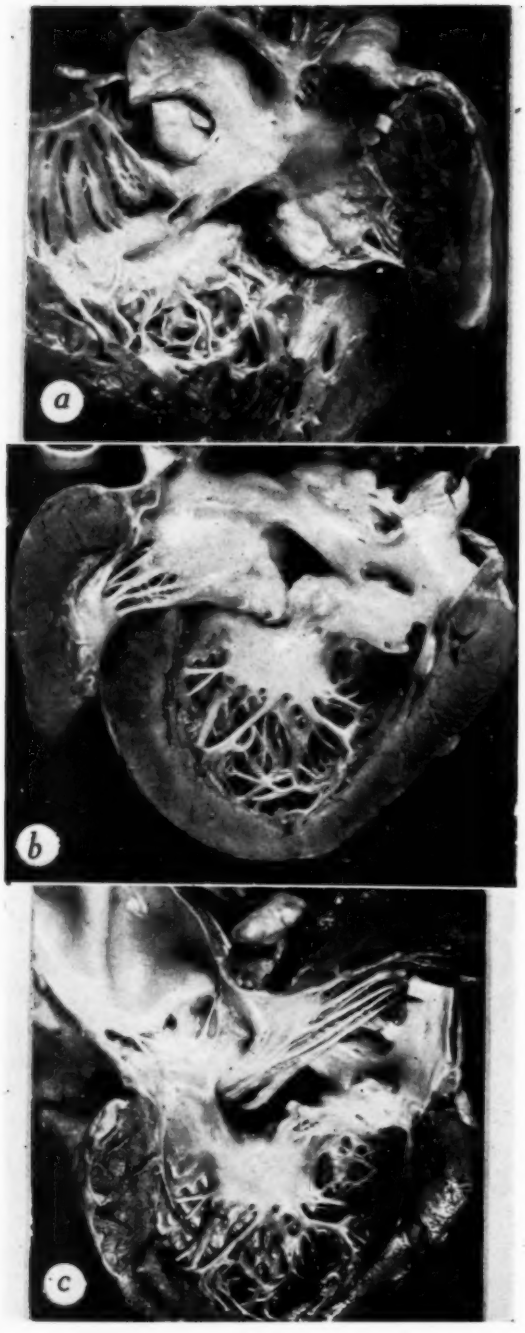

Fig. 2.—*a*, Interior of right side of heart in Case 1. The septal cusp of the tricuspid valve is cleft. The interatrial foramen primum is patent. The underlying portion of the interventricular septum shows a small defect. The right ventricular wall is thick. *b*, Interior of left side of heart in Case 1. The aortic cusp of the mitral valve is cleft. The chordae of the posterior half of this cusp are short and attached to the crest of the interventricular septum. The defects in the lower part of the interatrial septum and in the posterior portion of the interventricular septum are portrayed. *c*, Interior of left ventricle in heart in Case 1. The defect in the upper posterior portion of the interventricular septum is continuous with a defect in the posterior portion of the membranous portion of the interventricular septum. The right cusp of the aortic valve is fenestrated.

The chordae tendineae of the anterior cusp of the common atrioventricular valve were attached as follows: The right half of this cusp was attached by chordae to an anterior papillary muscle in the right ventricle. The left half was attached by chordae to an anterior papillary muscle in the left ventricle. The anterior face of the large anterior cusp lay immediately behind the upper anterior portion of the interventricular septum and the conus regions of the ventricles. It was, however, not attached to any of these structures. The posterior cusp of the common atrioventricular valve was smaller than the anterior one. The lateral chordae of this cusp were attached either to small posterior papillary muscles in each ventricle or directly to unspecialized areas in the ventricular walls (Fig. 2,*a* and *b*). In the region of the midline of the heart, the posterior cusp of the common atrioventricular valve was attached by very short chordae to the crest of the underlying posterior portion of the interventricular septum. Because of this intimate attachment, it was obvious that the degree of excursion of the posterior cusp must have been limited.

The shape of the ostium of the common atrioventricular valve was roughly that of two letter T's placed end to end in such a way that the two vertical limbs ran from right to left. The upper horizontal limb of one T lay in the right side of the heart and the other in the left (Fig. 1). Immediately above the ostium of the common atrioventricular valve, there was a sickle-shaped defect in the interatrial septum. The height of this defect was 1.0 centimeter. Below the common atrioventricular valve, there was a concave defect in the posterior muscular portion of the interventricular septum (Figs. 1 and 2,*a* and *b*). The height of this defect was 0.6 centimeter.

More anteriorly, that portion of the interventricular septum which lay immediately in front of the large anterior cusp of the common atrioventricular valve was somewhat defective. This defect, when viewed from behind, was concave, and it involved the membranous portion of the interventricular septum (Fig. 2,*c*).

The region of the fossa ovalis was normally developed. The foramen ovale was functionally closed but was patent to a probe. The ductus arteriosus was closed. The chambers of the right atrium and ventricle were dilated. The great vessels were normally related to each other and to the heart. The pulmonary artery was relatively wide and measured 3.5 cm. in circumference. The aortic orifice measured 2.5 cm. in circumference. The walls of both ventricles were hypertrophic. Each measured 0.5 cm. in thickness.

The coronary arteries arose normally. The marginal branch of the right artery was prominent, a feature characteristic of hearts exhibiting right ventricular hypertrophy. The great veins drained into the proper atria. No anomalies were found by examination of the rest of the body. The lungs contained small foci of bronchopneumonia. Throughout the lungs, in pneumonic portions and elsewhere, there was a considerable degree of engorgement and tortuosity of the capillaries of the alveolar walls. The arterioles had thick walls, mainly as the result of an increased number of smooth muscle cells within the media. These were concentrically arranged. Examination of the medium-sized arteries revealed hypertrophy of the media and an abundance of elastic fibers in the intima and media. Changes involving the alveolar capillaries and the pulmonary vessels were not observed in control sections obtained from infants of similar age who had died of causes other than cardiac disease.

Microscopic examination of the liver revealed congestion associated with a mild degree of parenchymal atrophy at the centers of the lobules. Sections of the myocardium did not reveal any lesions.

CASE 2.—A white girl, aged 5 months, was admitted to the hospital on March 25, 1943, because of respiratory distress. Shortly after birth, which had occurred at full term, it was noticed that the infant was cyanotic. After this, cyanosis occurred intermittently and was precipitated by feeding or crying. Development was slow and the child could not hold up her head until she was 4 months of age. Examination revealed marked cyanosis, respiratory distress, and fever. There were bilateral pulmonary râles. No cardiac murmur was heard. The facies, hyperflexibility of the fingers, and the thick, protruding tongue supported the opinion that mongolism was present. The infant had an umbilical hernia. Laboratory studies revealed a moderate degree of anemia. The value for the hemoglobin was 9.2 Gm. per 100 c.c. of blood.

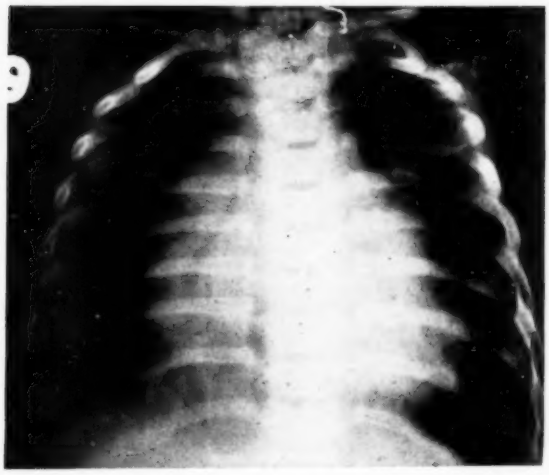

Fig. 3.—Roentgenogram of thorax showing cardiac enlargement in Case 2.

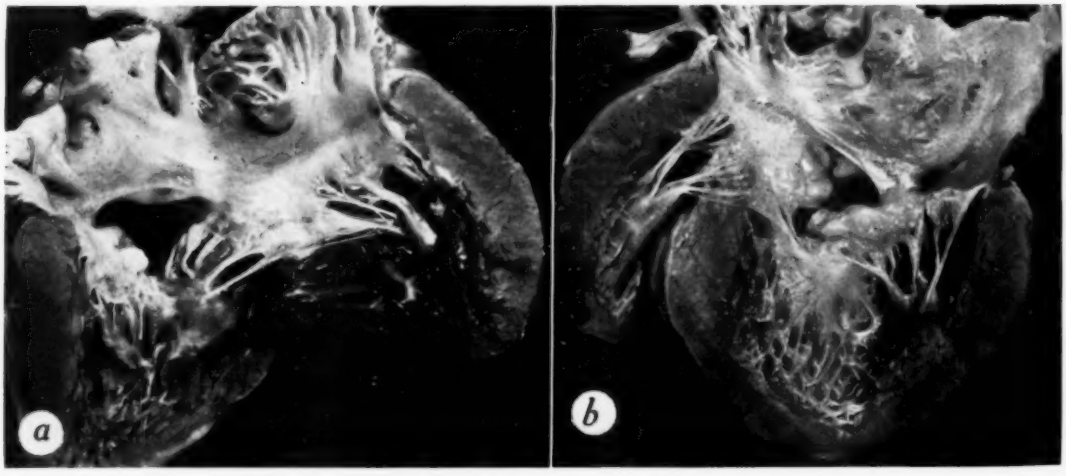

Fig. 4.—*a*, Right side of heart in Case 2. The septal cusp of the tricuspid valve is cleft. There is patency of the interatrial foramen primum. A small defect is present in the underlying posterior portion of the interventricular septum. A small portion of the anterior half of the cleft aortic cusp of the mitral valve can be seen through the interatrial septal defect (see *b*). This together with the anterior portion of the cleft tricuspid cusp forms the anterior cusp of the common atrioventricular valve. Some of the chordae of this cusp are attached to the upper portion of the interventricular septum. The wall of the right ventricle is hypertrophic. *b*, Left side of heart in Case 2. The aortic cusp of the mitral valve is cleft. The posterior half of this cusp is intimately connected to the crest of the underlying interventricular septum by short chordae. The interatrial foramen primum is patent. There is a small defect in the underlying interventricular septum.

Blood counts revealed 3,640,000 erythrocytes and 24,200 leucocytes per cubic millimeter of blood. Urinalysis did not disclose any abnormality. A flocculation test for syphilis, performed on the serum, was negative. Roentgenologic examination of the thorax disclosed cardiac enlargement which suggested the presence of congenital cardiac disease (Fig. 3). While under observation, the infant became increasingly cyanotic and died two days after admission to the hospital.

Necropsy disclosed cardiac anomalies which were virtually identical with those observed in Case 1 (Fig. 4,*a* and *b*). There was persistence of the common atrioventricular canal which was guarded by a single valve. Interatrial and interventricular septal defects likewise were similar to those seen in the heart in Case 1. Unlike the situation in Case 1, the large anterior leaflet of the common atrioventricular canal was attached to the posterior aspect of the membranous portion of the interventricular septum. The region of the fossa ovalis was normally developed. The foramen ovale was patent to a probe but was not functionally patent. The ductus arteriosus was closed. The heart was enlarged; it weighed 41 grams in contrast with an estimated normal weight of 21 grams.

A moderate degree of dilatation of the right atrium and ventricle was present. The wall of the right ventricle was hypertrophic and measured 0.7 cm. in thickness; the wall of the left ventricle was 0.8 cm. thick. The circumference of the orifice of the pulmonary artery measured 3.0 cm.; that of the aorta measured 2.5 centimeters. As in Case 1, the marginal branch of the right coronary artery was wide and prominent. The pulmonary artery and aorta were properly related to each other and to the ventricles. The pulmonary veins drained into the left atrium, and the venae cavae and coronary sinus drained into the right atrium.

Microscopically, all of the pulmonary lobes contained patches of lipoid pneumonia which alternated with regions in which no pneumonic process was present. Examination of latter regions revealed considerable degrees of engorgement and tortuosity of the alveolar capillaries. The arterioles throughout the lungs showed thickened media identical with those in Case 1, and the medium-sized arteries showed medial hypertrophy and an increase in elastic tissue as in Case 1. The liver showed evidence of a mild degree of chronic passive congestion. The mesentery of the descending colon was unduly long, which caused a redundancy of this segment of intestine. Otherwise, no congenital or acquired lesions were observed in the abdominal organs.

CASE 3.—This patient was a 2½-month-old white girl. She was said to have been a full-term infant, but weighed only 5 pounds and 14 ounces (2.7 kg.) at birth. Four days after birth, jaundice had developed. The jaundice had remained apparent for one week and then had disappeared spontaneously. The infant had left the hospital when she was nine days old. At home, she had nursed poorly and had not gained weight at a normal rate.

On Jan. 29, 1947, when the infant was 2½ months of age, she was admitted to the hospital because she was extremely malnourished. At that time, she was febrile. No cyanosis was present. A blowing systolic murmur was heard over the base of the heart. Roentgenologic examination of the thorax revealed an enlarged heart and evidence of pneumonia in the upper lobe of the right lung (Fig. 5). There were no positive physical signs referable to the lungs, however. On the day after she was admitted to the hospital, her temperature was normal. A slight degree of cyanosis was first noticed at that time. The value for the hemoglobin was 9.4 Gm. per 100 c.c. of blood. Blood counts revealed 2,730,000 erythrocytes and 9,800 leucocytes per cubic millimeter of blood. She failed progressively and died two days after her admission to the hospital.

Necropsy revealed a series of cardiac anomalies virtually identical with those found in Cases 1 and 2 (Fig. 6,*a* and *b*). In addition, the region of the fossa ovalis was anomalous and a functionally patent foramen ovale was present.

As in Cases 1 and 2, a common atrioventricular canal was guarded by a single valve, and the lower interatrial septum and upper posterior interventricular septum were defective. The defect in the lower interatrial septum measured 1.8 cm. from before backward and 0.9 cm. in height at its middle point. The defect in the interventricular septum was small and measured about 0.2 cm. in height. The chordae of the posterior cusp of the common atrioventricular valve were short and fused to the crest of the underlying interventricular septum. The upper limbus of the fossa ovalis was normally developed but the lower limbus was absent (Fig. 6,*a*). The valve of the foramen ovale was short and created a functional patency of the foramen ovale (Fig. 6,*b*).

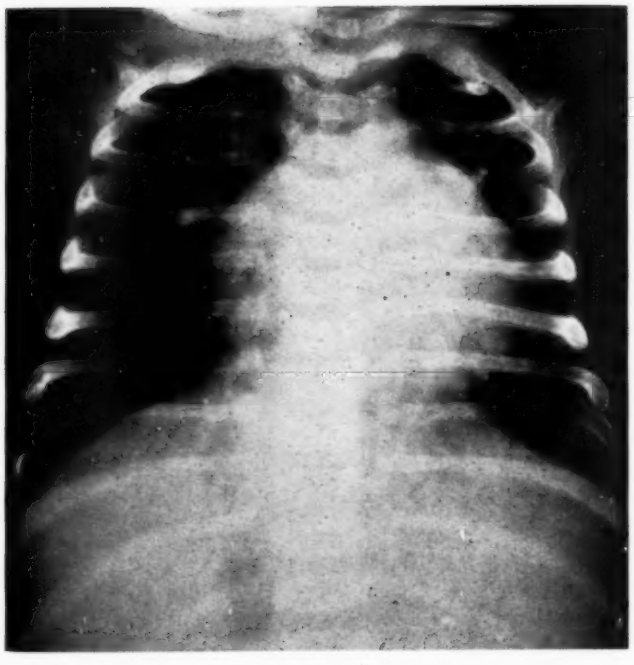

Fig. 5.—Roentgenogram of thorax in Case 3 showing cardiac enlargement and evidence of pneumonia in the upper lobe of the right lung.

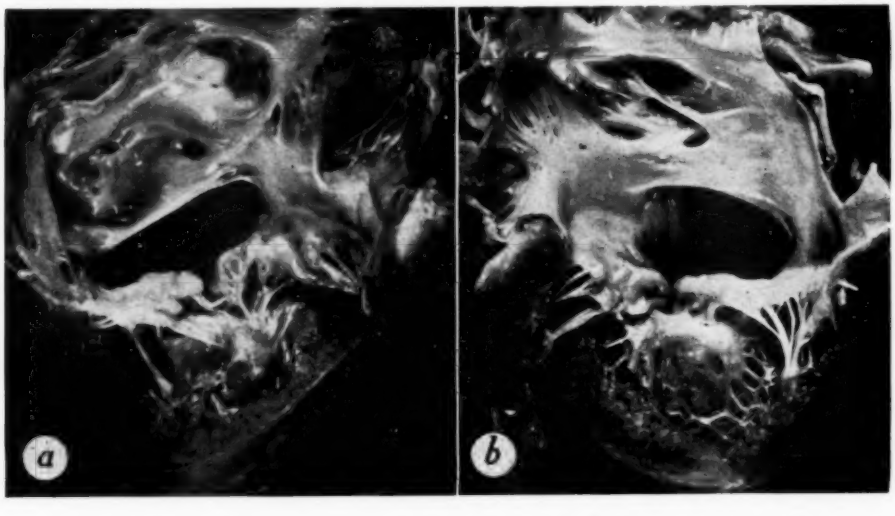

Fig. 6.—*a*, Right side of heart in Case 3. The septal cusp of the tricuspid valve is cleft. Each half is attached by short chordae to the underlying interventricular septum. The defect in the lower interatrial septum represents patency of the interatrial foramen primum. The foramen ovale shows a small zone of patency. The right ventricular wall is thick. *b*, Interior of left side of heart in Case 3. The aortic cusp of the mitral valve is cleft. The anterior half of the cleft septal cusp of the tricuspid valve can be seen through the lower interatrial septal defect (see *a*). It is continuous with the anterior half of the cleft aortic mitral cusp. Together, these form the elements of the large anterior cusp of the common atrioventricular valve. The chordae of the posterior half of the cleft mitral valve are short and their lower ends are attached to the crest of the interventricular septum. A short valve of the foramen ovale creates a patency of the foramen.

The average diameter of this opening was 0.3 centimeter. As in the two previous hearts, the right atrium and ventricle were dilated and the wall of the right ventricle was moderately thick (0.3 cm.). The wall of the left ventricle was 0.6 cm. thick. The orifice of the pulmonary artery was somewhat dilated and measured 3.0 cm. in circumference. The aortic orifice measured 2.5 cm. in circumference. The ductus arteriosus was closed. The aorta and pulmonary artery were properly placed. The pulmonary veins, venae cavae, and coronary sinus drained into the proper atria.

Microscopic examination of the lungs revealed scattered small foci of pneumonia in early and resolving stages. The media of the pulmonary arterioles was hypertrophic and the alveolar capillaries were distended and tortuous. There was hemosiderosis of the liver, but definite evidence of chronic passive congestion of this organ was not observed. There was no anomaly of the abdominal organs.

CASE 4.—A white boy, 6 months of age, was admitted to the hospital on June 15, 1941, because of cyanosis and respiratory embarrassment. At the time of his birth, it was evident that the infant was afflicted with mongolism and that he was constantly cyanotic. A precordial systolic murmur was first observed when the infant was 8 days old.

One month before his admission to the hospital, a respiratory infection developed and caused an intensification of the cyanosis. The symptoms of this infection persisted. When the child was admitted to the hospital, physical examination revealed fever, cyanosis, a precordial systolic murmur, and evidence of pneumonia in the lower lobe of the right lung. The child died on the day of his admission to the hospital.

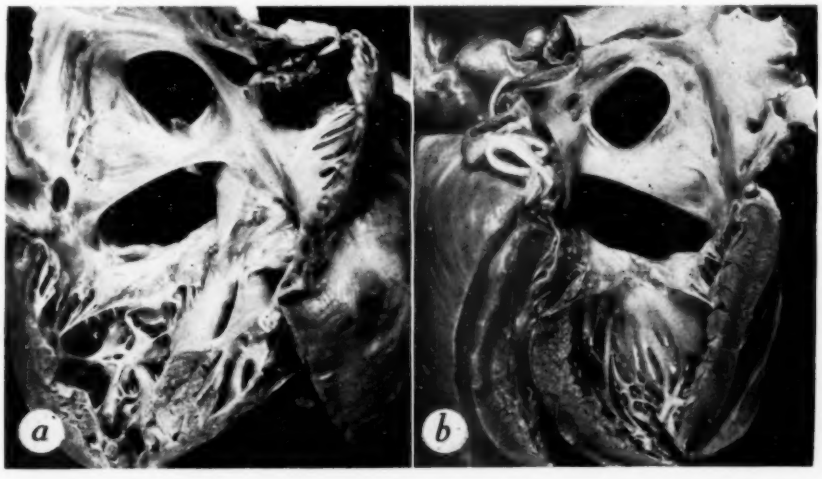

Fig. 7.—*a*, Interior of right side of heart in Case 4. The septal cusp of the tricuspid valve is intact. There are two defects in the interatrial septum. The lower one represents a patent interatrial foramen primum; the upper one represents a patent foramen ovale. There is a recognizable degree of hypertrophy of the right ventricle. *b*, Interior of left side of heart in Case 4. The aortic cusp of the mitral cusp is cleft except at its very base. The interatrial defects seen from the right (*a*) are evident. The patency of the foramen ovale appears to have resulted from complete absence of the valve of the foramen ovale.

At necropsy the heart was found to be considerably enlarged. It weighed 88 grams. (The average normal weight of the heart in a male infant of six months is about 23 grams.) When the heart was opened, two interatrial septal defects were encountered. One involved the region of the fossa ovalis and represented a patent foramen ovale. The other defect was present in the lower region of the interatrial septum and was similar in position and shape to the interatrial septal defects observed in Cases 1, 2, and 3 (Fig. 7,*a* and *b*). The superior and inferior limbi

of the fossa ovalis were properly developed. The valve of the foramen ovale was not identifiable. This condition accounted for the patency of the foramen ovale. The opening measured 1.0 cm. from before backward and 0.6 cm. from above downward.

The upper margin of the defect in the lower interatrial septum was sickle shaped. The defect lay immediately superior to the atrioventricular valves which formed the lower border of the opening in the septum. This defect measured 1.6 cm. from before backward and 1.4 cm. from above downward. In contrast with the condition found in Cases 1, 2, and 3, the atrioventricular canal had been divided into right and left halves; the right half was guarded by an essentially normal tricuspid valve (Fig. 7,*a*). The left half of the divided atrioventricular canal was guarded by the mitral valve which, unlike the tricuspid valve, was improperly formed. The anomaly of the mitral valve consisted of a cleft which involved all of the anterior or aortic cusp except the base (Fig. 7,*b*). The anterior half of the cleft cusp was joined to the left anterior papillary muscle by chordae tendineae. The posterior half of this cusp was attached to the posterior wall of the left ventricle by chordae. While it was evident that this heart had both mitral and tricuspid valves, the two components of the anterior cusp of the mitral valve and the septal cusp of the tricuspid valve were continuous with each other below the defect in the lower part of the interatrial septum.

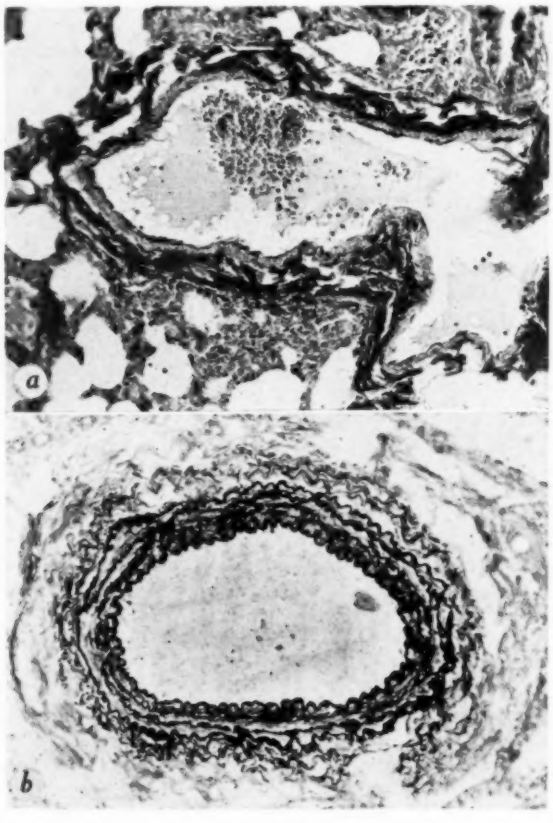

Fig. 8.—*a*, Photomicrograph of a normal small pulmonary artery of a girl 7 months of age who died of hydrocephalus. There is a fine lamina of elastic tissue in the intima but there is no elastic tissue in the media. Section was stained with Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain (reduced from ×125). *b*, Photomicrograph of a small pulmonary artery in Case 4. An abundance of elastic tissue is present in the somewhat hypertrophied media. Compare this artery with normal artery of similar size in *a*. Section stained with Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain (reduced from ×125).

A considerable degree of dilatation of the right chambers of the heart and of the left ventricle was present. The walls of both ventricles were hypertrophic; the wall of the right ventricle was 0.5 cm. thick and that of the left ventricle was 0.6 cm. thick.

The pulmonary artery and the ascending aorta were normally placed and inter-related. There was a moderate degree of dilatation of the pulmonary artery. The circumference of its orifice measured 3.5 cm.; that of the aorta measured 2.5 centimeters. The veins were joined normally with the atria.

Microscopic examination of the lungs revealed scattered foci of intra-alveolar foam cells, a picture consistent with that of resolving pneumonia. In addition, the examination disclosed hypertrophy of the media of the arterioles and tortuosity and engorgement of the alveolar capillaries. These changes were similar to those observed in Cases 1, 2, and 3. The media of the intrapulmonary arteries was hypertrophic and contained an abundance of elastic tissue (Fig. 8,*a* and *b*). Microscopic examination of the liver revealed a mild degree of central congestion but there was no definite evidence of central parenchymal atrophy.

A Meckel's diverticulum was present and a focus of heterotopic pancreatic tissue was found in the wall of the jejunum. Examination of the abdomen did not disclose any other abnormality.

CASE 5.—The patient was a white businessman, aged 36 years. When he was first observed at the clinic on Sept. 10, 1938, he stated that for one month he had suffered from dyspnea on slight exertion and from edema of the ankles. He also related that he was known to have had a cardiac murmur since the age of 2 years. There was no history of rheumatic fever. Physical examination revealed that his heart was enlarged; its rhythm was regular and its rate was 96 beats per minute. There was a loud systolic murmur which was loudest over the cardiac apex and was transmitted to the left axilla. Roentgenographic examination of the thorax showed cardiac enlargement, a prominent pulmonary conus, and pulmonary congestion (Fig. 9). The patient was dismissed from the clinic on Oct. 27, 1938.

He returned to the clinic on Feb. 13, 1939. At that time, he was acutely ill and stated that about three months before, he had begun to suffer from generalized aching pains which were associated with a daily rise in temperature of 0.5° Fahrenheit. About one month after the onset of these symptoms, the fever became a prominent feature of his illness. This occurred in episodes, during which his temperature would rise to 103° Fahrenheit. The patient was acutely ill, febrile, cyanotic, and dyspneic. There was a distinct systolic murmur over the cardiac apex, and one observer thought that an apical diastolic murmur also could be heard. No thrill was present. The heart was enlarged and its rate was 120 beats per minute. The cardiac rhythm was regular. Numerous moist pulmonary râles were heard. These were interpreted as evidence of pulmonary congestion. The liver was palpable and the ankles were edematous.

A blood culture disclosed a green-producing *Streptococcus*. The value for the hemoglobin was 8.7 Gm. per 100 c.c. of blood. There were 3,020,000 erythrocytes and 9,000 leucocytes per cubic millimeter of blood. Urinalysis revealed albuminuria Grade 1, on the basis of 1 to 4, and an occasional erythrocyte. The patient's respiratory distress became progressively more evident, and he died on Feb. 19, 1939.

The heart was enlarged and weighed 575 grams. There was a defect in the lower interatrial septum, the upper margin of which was crescent shaped (Fig. 10,*a* and *b*). The defect measured 4.0 cm. from before backward and 3.0 cm. from above downward. Examination of the aortic leaflet of the mitral valve revealed a cleft which was similar to that seen in the heart in Case 4 (Fig. 10,*b*). The anterior half of the cleft aortic cusp of the mitral valve was intimately attached to the underlying interventricular septum by a series of short, stout chordae tendineae. The posterior half of this cusp was attached by thin chordae of normal caliber to the left posterior papillary muscle. The septal tricuspid cusp was properly formed (Fig. 10,*a*). As in Case 4, the bases of this cusp and of the elements of the aortic cusps of the mitral valve were continuous beneath the defect in the lower interatrial septum.

One feature not seen in the hearts in the four other cases in this series was the presence of large, friable, endocardial vegetations characteristic of subacute bacterial endocarditis. These were deposited on the atrial surfaces of both halves of the cleft aortic cusp of the mitral valve.

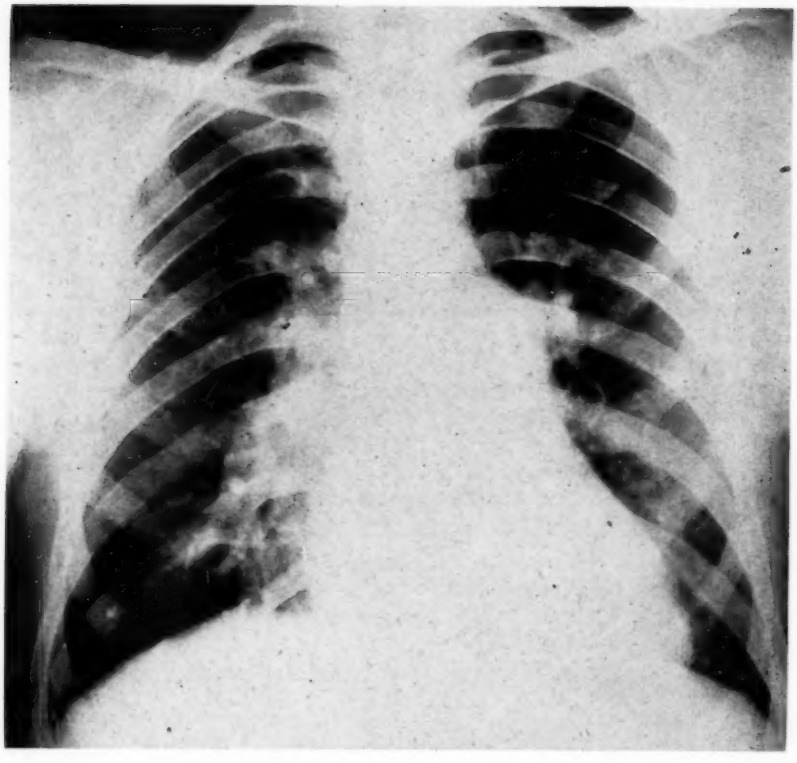

Fig. 9.—Roentgenogram of thorax in Case 5 showing cardiac enlargement, a prominent pulmonary conus, and pulmonary congestion.

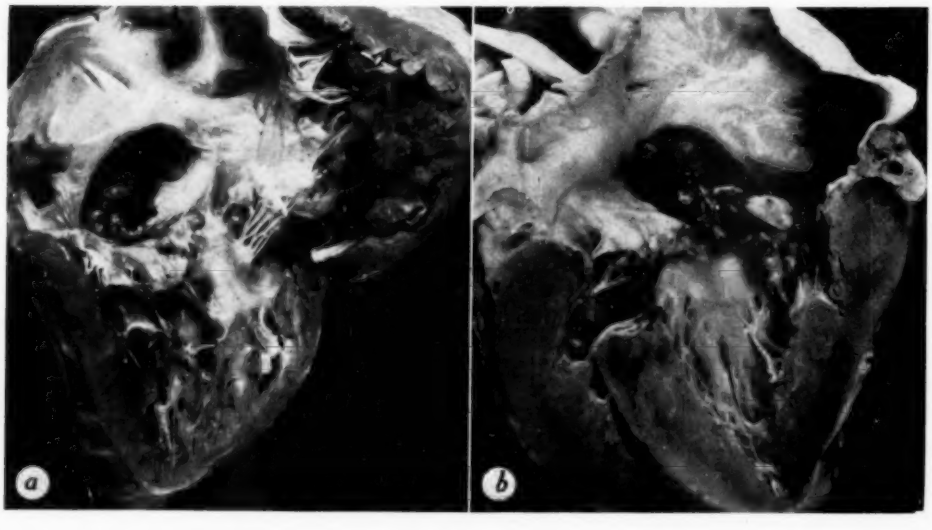

Fig. 10.—*a*, Interior of right side of heart in Case 5. The septal cusp of the tricuspid valve is intact. A large defect is present in the lower interatrial septum. Through this the vegetations of subacute bacterial endocarditis may be seen. The foramen ovale is functionally closed. The wall of the right ventricle is hypertrophic. (From Tinney and Barnes.[2]) *b*, Interior of left side of the heart in Case 5. The aortic cusp of the mitral valve is cleft. It is similar to the aortic cusp in Case 4. Compare with Fig. 7, *b*. Large vegetations of subacute bacterial endocarditis are attached to the posterior half of the cleft aortic cusp of the mitral valve. The lower interatrial septum is the site of a large defect.

From this position, the vegetations had extended for a short distance onto the adjacent septal tricuspid cusp (Fig. 10,*a* and *b*).

The region of the fossa ovalis was normally developed. The foramen ovale was patent to a probe but functionally closed. The chambers of the right atrium and the right ventricle, including the subpulmonary region, were dilated. The circumferences of the four cardiac valves measured as follows: tricuspid, 14.0 cm.; mitral, 11.0 cm.; pulmonary, 10.0 cm.; and aortic, 5.5 centimeters.

Each ventricular wall was hypertrophic; the wall of the right ventricle was 0.6 cm. thick, and that of the left ventricle was 1.8 cm. thick. The relations of the great vessels to the heart were normal. The marginal branch of the right coronary artery was wide. There was no appreciable degree of atherosclerosis of the coronary arteries.

Microscopically, the endocardial vegetations were composed of fibrin which contained leucocytes and colonies of streptococci. There were septic infarcts in the lungs, left kidney, and spleen. Examination of the lungs also revealed a considerable degree of engorgement of the alveolar capillaries. There was chronic passive congestion of the liver.

There were two retroperitoneal abscesses, one near the pancreas and the third portion of the duodenum, the other in the right flank. Grossly, these were filled with semisolid caseous material. Microscopically, the walls of these cavities resembled healing stages of nonspecific abscesses. No bacteria were identified in these lesions.

COMMENT

The atrioventricular regions in the hearts in Cases 1, 2, and 3 were virtually identical. The essential anomalies in each heart consisted of a defect in the lower portion of the interatrial septum, a defect in the superior aspect of the posterior region of the interventricular septum, and failure of formation of the right and left halves of the atrioventricular canal. The persistent single atrioventricular canal was guarded by one valve which was common to both sides of the heart. The large anterior cusp of this valve was composed of those elements which normally became the anterior halves of the septal cusp of the tricuspid valve and of the anterior or so-called aortic cusp of the mitral valve. Similarly, the posterior cusp of the common atrioventricular valve was composed of tissue which normally is represented by the posterior halves of the septal cusp of the tricuspid valve and the aortic cusp of the mitral valve. The lateral cusps of the common valve represented the anterior and posterior tricuspid and posterior mitral cusps.

The essential anomalies in the hearts in Cases 4 and 5 consisted of a cleft in the anterior or so-called aortic cusp of the mitral valve. The septal cusp of the tricuspid valve was intact. The tissue of the aortic cusp of the mitral valve and that of the septal cusp of the tricuspid valve were continuous beneath the defect in the lower interatrial septal defect which was present in each of these hearts.

In Case 4, there was an additional interatrial septal defect. This was situated above the defect in the lower interatrial septum, to which reference has already been made, and it represented a widely patent foramen ovale. An unusually short valve of the foramen ovale created this defect. In Case 3, the region of the fossa ovalis was likewise defective. In this case, the lower limbus of the fossa ovalis was absent and the foramen ovale was patent on the basis of a short valve. It should be emphasized that the anomalies in the region of the fossa ovalis seen in Cases 3 and 4 were not related to the defects in the

lower interatrial septum and in the atrioventricular valves. We are interpreting these as additional, nonrelated anomalies.

Case 5 previously was reported by Tinney and Barnes[2] as a case of Lutembacher's disease, that is, a combination of mitral stenosis and interatrial septal defect. Re-examination of the heart in this case and a comparison of the pathologic findings with those in Cases 1, 2, 3, and 4 caused us to conclude that the valvular anomaly in this case was congenital and essentially identical with that in Case 4. Each of these anomalies represents a lesser degree of the lesion which occurred in complete form in Cases 1, 2, and 3.

It is of interest to consider the abnormalities in cardiac development which form the basis of the anomalies which are the subject of this paper. An excellent review of this subject was presented in 1927 by Gunn and Dieckmann.[3] The pertinent features may be summarized as follows: During the early life of the human embryo, two endocardial elevations, one dorsal and one ventral, appear at the junction of the single atrium and ventricle, that is, in the so-called atrioventricular canal. These elevations are known as the ventral and dorsal atrioventricular endocardial cushions. They grow in the midline of the atrioventricular canal and ultimately come into contact with each other and fuse. By so doing, the atrioventricular endocardial cushions divide the atrioventricular canal into right and left halves. While the described changes are taking place, two important structures are developed, one in the primitive atrium, the other in the primitive ventricle. These are the primary interatrial septum and the muscular interventricular septum. The former grows downward from the superior and dorsal walls of the atrium. As it grows, the primary interatrial septum narrows the communication between the two atria which is called the "interatrial foramen primum." Eventually the lower margin of the primary interatrial septum comes into contact with the upper surface of the fused ventral and dorsal atrioventricular endocardial cushions and blends with these to complete the formation of the lower portion of the interatrial septum. The effect of this development is that the interatrial foramen primum is closed. The details concerned with the development of the secondary interatrial septum and of the region of the fossa and and foramen ovale are out of the scope of this paper and will not be reviewed herein. The interested reader is referred to the works of Patten[4] and others on that subject.

The muscular portion of the interventricular septum grows upward from its anlage near the ventricular apex progressively to narrow the communication between the two ventricles. Posteriorly, the interventricular septum ultimately joins the lower aspects of the fused endocardial cushions to close the communication between the two ventricles in this region. Gunn and Dieckmann suggested that the united endocardial cushions send prolongations downward to meet and fuse with the posterior portion of the interventricular septum in order to complete the separation of the posterior portions of the two ventricles. It has not been proved, however, that the cushions take part in this division, other than mere union with the fully developed interventricular septum.

The anlagen of the anterior halves of the aortic cusp of the mitral valve and the septal cusp of the tricuspid valve lie in the ventral atrioventricular endocardial cushion while the anlagen of the posterior halves of these two cusps lie in the dorsal cushion.[5] If fusion of the endocardial cushions takes place normally, the anterior and posterior anlagen of the aortic cusp of the mitral valve are united and an intact, noncleft leaflet develops. A similar situation applies to the septal tricuspid leaflet.

Should the ventral and dorsal atrioventricular endocardial cushions fail to fuse, the atrioventricular canal will remain single or undivided. Moreover, the ventral and dorsal atrioventricular endocardial cushions will develop into the anterior and posterior cusps of the common atrioventricular canal. Failure of fusion of the atrioventricular endocardial cushions appears to be the explanation for the valvular anomalies in Cases 1, 2, and 3. When the hearts of these patients were opened and examined in the conventional manner, the aortic cusp of the mitral valve and the septal cusp of the tricuspid valve were found to be cleft. The anterior halves of each of these two cusps were continuous and formed the anterior cusp of the common atrioventricular valve. Similarly, the posterior halves of these same cusps were continuous and represented the posterior cusp of that valve.

The reader will appreciate that the valvular anomaly that was present in Cases 1, 2, and 3 represents the result of complete failure of fusion of the ventral and dorsal atrioventricular endocardial cushions. From the basic concept exemplified by these three specimens, one may then study the hearts in Cases 4 and 5 more comprehensively. In these, the septal cusp of the tricuspid valve was not cleft and the atrioventricular canal had been divided into right and left halves. Nevertheless, the aortic cusp of the mitral valve, except at its base, was cleft. This can only be explained as a failure of complete fusion of the ventral and dorsal atrioventricular endocardial cushions, the complete fusion of which is necessary for the creation of a properly formed aortic cusp of the mitral valve. It seems justifiable, therefore, to conclude that in Cases 4 and 5, in spite of the absence of a single atrioventricular canal, the lesions were the same, although not so completely developed as they were in Cases 1, 2, and 3.

From the description of the formation of the lower interatrial septum presented herein, it is evident that the defect of the lower interatrial septum seen in all of the five cases may be termed "patency of the interatrial foramen primum." It is further evident that the defect need not entirely, if at all, be attributed to a failure on the part of the septum primum to develop fully. The defect may have resulted from a deficient growth of the atrioventricular endocardial cushions which would be responsible not only for failure of proper fusion of these cushions but also for a failure to meet the downgrowing septum primum. The initial defect of the lower interatrial septum may have been small at one time, but since the septum primum did not become anchored below, the size of the defect undoubtedly increased with the progressive growth in the size of the heart.

The defects in the posterior portions of the interventricular septum which were present in Cases 1, 2, and 3 seem to result from a deficient growth of the in-

terventricular septum. It cannot, however, be denied with any degree of finality that these defects, too, are caused by a deficiency of growth of the atrioventricular endocardial cushions. It is appreciated that, in the normally developing heart, the posterior portion of the interventricular septum joins the fused atrioventricular endocardial cushions. Undersized endocardial cushions might fail to join with a normally developed interventricular septum. Moreover, as in the case of the defect of the lower interatrial septum, the size of the defect in the interventricular septum might very well increase with growth of the heart. That failure of fusion of the atrioventricular endocardial cushions may play a role in causing the defect of the posterior portion of the interventricular septum is supported by these five cases. In Cases 1, 2, and 3, in which failure of fusion of the endocardial cushions was complete, a defect of the underlying interventricular septum was found. On the other hand, in Cases 4 and 5, while fusion of the endocardial cushions was not complete, a considerable degree of fusion had occurred. In these cases, defects of the posterior interventricular septum, as seen in Cases 1, 2, and 3, were not observed.

In Case 1, the posterior aspect of the membranous portion of the interventricular septum was defective. The anterior cusp of the common atrioventricular valve was not attached to the conus regions of the ventricles. These two features are inter-related. In the normally developing heart, a swelling of the right side of the ventral atrioventricular endocardial cushion, known as the "right tubercle," makes a contribution to the structure of the posterior aspect of the membranous portion of the interventricular septum.[6] In this way the septal cusp of the tricuspid valve, the anterior portion of which is derived from the right side of the ventral atrioventricular endocardial cushion, is united with the membranous portion of the interventricular septum in normal hearts. In Case 1, the membranous septal defect and the failure of attachment of the anterior cusp of the common atrioventricular valve to the conus region of the ventricles can both be explained by a failure of the right tubercle of the ventral atrioventricular endocardial cushion to have developed normally.

In the cases herein reported, the defects must have created abnormal circulatory conditions. It will be recalled that in each specimen there was dilatation of the right cardiac chambers and of the pulmonary artery. The pulmonary capillaries were engorged and tortuous. From this evidence, it seems correct to conclude that the right side of the heart and the pulmonary circulatory system carried more blood than they do normally. In this connection, the defective interatrial septum played an important part in each case. In Cases 4 and 5, this role must have been all important, while in Cases 1, 2, and 3, the added factor of a defective interventricular septum must have added to the abnormal circulatory conditions.

Under conditions of cardiac compensation, the pressure within the left side of the heart exceeds that within the right. In the presence of a defective interatrial septum with or without an interventricular septal defect, some of the blood entering the left heart from the lungs would be diverted through the septal defect or defects to the right side of the heart. Thus, some blood which had

passed through the pulmonary vessels would be recirculated through these without passing through the systemic system. An arteriovenous shunt within the lesser circulation would be in operation. The strain upon the right side of the heart caused by this shunt would result in right-sided hypertrophy and ultimately, in failure. In that event, the pressure of the blood in the right side of the heart might exceed that in the left. This would explain the absent or transient cyanosis in some cases until relatively late in the disease. Whether the presence of a common atrioventricular valve, per se, created an added burden on the functional capacity of the heart is open to some debate. In Cases 1, 2, and 3, the posterior cusp of the common atrioventricular valve was intimately attached to the posterior aspect of the crest of the interventricular septum by short chordae tendineae. This phenomenon undoubtedly prevented any appreciable degree of upward excursion of the cusp concerned. As a result, the atrioventricular valve would not close completely during systole. Thus, in Cases 1, 2, and 3, the incompetent single atrioventricular valve with the lower interatrial septal defect must have allowed regurgitation of blood from the high-pressured left ventricle into the left atrium. This would increase the volume and pressure in the left atrium and add to the volume of aerated blood entering the right atrium through the interatrial septal defect.

In Cases 4 and 5, the major degree of functional abnormality appears to have been caused by defects of the interatrial septa. Nevertheless, it appeared that the valvular anomalies also must have played a role in causing embarrassment of cardiac function. The cleft aortic cusp of the mitral valve in each case must have been responsible for mitral regurgitation.

In Case 5, the regurgitation caused by the cleft aortic cusp of the mitral valve must have been augmented by anomalously attached short, thick chordae of the anterior half of this cusp. It will be recalled that these were short and bound the anterior half of the cleft aortic cusp of the mitral valve to the crest of the underlying posterior portion of the interventricular septum. The effect of the mitral regurgitation in Cases 4 and 5 undoubtedly was a marked increase in pressure within the left atrium. This phenomenon, in the presence of a defective interatrial septum, must have resulted in the flow of a great volume of blood from the left atrium into the right. The resulting strain upon the right side of the heart is evident.

Excellent illustrations of the structure of the common atrioventricular valve are to be found in Fig. 1 of Robson's article[7] and in Fig. 5 of the paper by Moragues.[8] To obtain these illustrations, the authors removed the roofs of the atria and detached the posterior attachment of the interatrial septum. The septum was reflected anteriorly and the photograph of the common atrioventricular orifice and valve was taken from above. Well illustrated is the common atrioventricular orifice guarded by large anterior and posterior cusps and several lateral cusps. One is impressed with the similarity of the picture with that of the common atrioventricular orifices seen normally in the hearts of very young embryos.[9] These illustrations served as the inspiration for the preparation of Fig. 1 of this paper.

Von Rokitansky,[10] in 1875, described two groups of hearts with cleft atrioventricular valves and defects in the lower interatrial septa. In one group, there was an associated defect of the upper posterior portion of the interventricular septum, and in the other group, the interventricular septum was not defective. In 1888, Schmaltz,[11] in a discussion of von Rokitansky's classification of these two groups of hearts, expressed the opinion that the distinction was artificial. Nevertheless, Abbott[1] maintained, in essence, the grouping of von Rokitansky. Cases in which there was no defect in the interventricular septum were classified as cases of persistent ostium primum with cleft mitral valve, and cases in which there was an added defect of the interventricular septum were classified as cases of persistent common atrioventricular ostium, or "incomplete double heart." We are in favor of the opinion of Schmaltz, namely, that the separation of these cases into two groups is artificial. In recalling the embryologic features of the defects under discussion, it is evident that the cleft of the aortic cusp of the mitral valve and of the septal cusp of the tricuspid valve represents persistence of the common atrioventricular canal and is the crucial point in classifying these cases. A defect in the lower interatrial septum, while not necessary for the diagnosis, is, nevertheless, practically always associated with, and undoubtedly represents, failure of union of the ventral and dorsal atrioventricular endocardial cushions with the septum primum.[8] On the other hand, a defect of the posterior portion of the interventricular septum is not always present, nor need it be, since the interventricular septum does not take part in dividing the primitive atrioventricular canal into right and left halves.

Abbott's employment of the term "incomplete double heart" for the lesion under discussion does not seem appropriate.[1] The word "double" would imply either a true duplication, such as one might expect in twining, or the attempt of formation of several hearts, as illustrated by Herxheimer.[12] The definitive heart, while two-sided, cannot truly be described as double. Were one desirous of retaining the word "incomplete," it would not be as misrepresentative of the lesion as the word "double," but the term "incomplete heart" would not connote the lesion as vividly as does the name "persistent common atrioventricular canal."

In Table I, we have tabulated the available pertinent data in fifty cases reported in the literature and in the five cases of persistent common atrioventricular canal with patent interatrial foramen primum which we are reporting. In this table, we have also indicated whether or not the reports contained illustrations of the hearts described. In this table we included only cases in which the lesion was described or illustrated in the reports. Accordingly, we have excluded from the table the three cases which Bredt[44] mentioned but did not describe. Likewise, we have not included the case of Philpott,[45] who, in a listing of types of cardiac anomalies in his collection, reported finding one example of persistent common atrioventricular ostium in a group of eighty cases. Gibson and Clifton[46] reviewed 1,950 consecutive cases in which necropsy was performed on infants and older children and found that congenital anomalies of the heart and great vessels were present in 105 (5.4 per cent) of the cases. They made a diagnosis of persistent ostium primum in one case and of persistent ostium

primum together with a defect of the interventricular septum in another. Mongolism was present in each of these cases, but the hearts were not described or illustrated. These two cases were not included in our tabulation. While we have, undoubtedly, not included all adequately reported cases, we feel that our review is relatively complete. Some of the cases listed were discovered inadvertently while the literature pertaining to other congenital cardiac lesions was being studied. Therefore, some other cases may have been overlooked because they were classified on the basis of other associated congenital cardiac anomalies present. In our search for reported cases, we have derived considerable aid from the bibliographies in the works of Abbott,[1,14-16] Gunn and Dieckmann,[3] and Robinson,[35] as well as from the bibliography of the 1,000 cases in Abbott's Atlas analyzed by Bauer and Astbury.[47] The work of Bauer and Astbury, which obviously represents many hours of painstaking labor and patience, is a most valuable contribution to the original reports of the cases collected in Abbott's classic work. Nevertheless, we are not in complete agreement with their listing of the cases of persistent common atrioventricular canal. In the first place, the cases are classified as cases of "incomplete double heart," a term which we believe is not the most desirable. Of the ten cases listed under this heading by Bauer and Astbury, we consider that those reported by Cassel,[48] Shattock,[49] Symington,[50] and Wright and Drake[51] are not examples of the lesion under consideration. Cassel's case would best be classified as a case of cor triloculare biatriatum; Shattock's case, as a case of cor biloculare; Wright and Drake's case, as a case of cor triloculare biatriatum with single arterial trunk; and Symington's case, as a case of atresia of pulmonary and tricuspid ostia. Gunn and Dieckmann[3] are credited with having reported only one case, namely, Case 1; yet Case 2, as well, is a typical example of persistent common atrioventricular canal. After making these corrections, we would accept seven of the ten cases as cases of persistent common atrioventricular canal. In their listing of cases under the heading "Defects auricular septum below," we feel that the cases of Abbott[13] (Case 2), Abbott and Kaufmann[16] (Case 2), Moore,[30] Peacock,[32] and Sternberg[40] represent examples of persistent common atrioventricular canal, making at least a corrected total of thirteen examples of this lesion in Abbott's 1,000 collected cases of congenital cardiac disease.

In 1941, Robinson[35] reviewed the literature on persistent common atrioventricular ostium. He stated that thirty-nine cases had been reported prior to the one case he reported in the same article. In arriving at the total of thirty-nine, Robinson included twenty-two cases to which reference was made in the review of Gunn and Dieckmann.[3] In this group there were sixteen cases which had been mentioned by Keith.[25] Fourteen of these cases had been reported by Keith and two by Griffith. A study of Keith's article revealed that none of his own fourteen cases were individually described, but the article contained two illustrations of a heart with persistent common atrioventricular canal and the text included a clear and accurate account of the features of the lesion. Of the cases reported by Keith, therefore, we have chosen to include in Table I only the one in which the anomaly was illustrated.

TABLE I. DATA IN FIFTY-FIVE CASES OF PERSISTENT COMMON ATRIOVENTRICULAR CANAL*

AUTHOR	AGE	SEX	MONGOLISM	CARDIAC ENLARGEMENT	MURMUR	CYANOSIS	ILLUSTRATED	COMMENT
Abbott [13]	10 mo.	M	+	+	+	0	+	
Abbott [14]	15 hr.	–	+	–	–	+	+	Bicuspid pulmonary valve
Abbott [15]	5 mo.	F	+	–	+	+	+	
Abbott and Kaufmann[16]	35 yr.	M	0	+	+	+	0	
Arnold[17]	42 yr.	M	0	+	+	+	0	
Ash, Wolman, and Bromer[18] (Case 12)	3 mo.	–	–	+	+	+	0	
Ash, Wolman, and Bromer[18] (Case 13)	11 mo.	–	–	+	+	+	0	
Beattie[19]	Infant	–	–	0	–	+	+	Bulboventricular version; corrected transposition of great vessels; atresia of pulmonary artery; situs inversus of viscera
Benjamin, Landt, and Zeek[20]	18 mo.	F	0	+	+	+	+	Narrow pulmonary artery and small right ventricle; extreme degree of cyanosis; clubbing of fingers
Dublizkaja[21] (Case 2)	3.5 mo.	M	+	+	0	0	0	Patent ductus arteriosus
Dublizkaja[21] (Case 3)	2 mo.	–	–	+	+	+	+	
Goetsch[22]	18 mo.	F	+	+	+	+	+	Dextroposition of aorta; wide pulmonary artery; infantile coarctation of aorta; patent ductus arteriosus; subacute bacterial endocarditis
Gunn and Dieckmann[3] (Case 1)	1 yr.	F	+	+	+	0	+	Patent foramen ovale
Gunn and Dieckmann[3] (Case 2)	4 mo.	F	+	0	+	+	+	Patent ductus arteriosus; absence of lower limbus of fossa ovalis
Hart[23] (Case 12)	2 yr.	M	–	+	–	–	0	
Jaffe[24]	22 yr.	F	0	+	–	0	0	Anomalies of veins and of aorta; no anomaly of heart, per se
Keith[25]	—	–	–	–	–	–	+	No anomalies recognized in illustrations
Leech[26]	3 mo.	F	+	+	+	–	0	Anomalies of great vessels
Meeker[27]	1 yr.	F	+	+	–	–	+	
Mönckeberg[28] (Case 1)	10 mo.	M	+	+	+	+	+	
Mönckeberg[28] (Case 2)	2 days	M	–	–	–	–	0	
Mönckeberg[29]	9 mo.	M	–	+	–	+	0	Septum secundum not identified
Moore[30]	17 yr.	F	–	–	+	+	0	Thickening of mitral valve suggestive of rheumatic fever

Moragues[8]	16 mo.	M	0	+	+	+	+	
Patten[31]	1 or 2 yr.	—	–	–	–	–	+	
Peacock[32]	10 or 11 yr.	F	–	–	–	–	0	
Plauchu and Gardere[33]	2.5 mo.	M	–	+	+	–	0	Tetralogy of Fallot; bicuspid pulmonary valve
Preisz[34] (Case 3)	7 days	F	–	–	–	–	0	
Preisz[34] (Case 4)	5 days	M	–	–	–	–	0	Bicuspid pulmonary valve
Robinson[35]	6 mo.	M	+	+	0	+	+	
Robson[7]	4.75 yr.	M	0	+	+	+	+	
Rogers and Edwards (Case 1)	5 mo.	M	+	+	–	+	+	
Rogers and Edwards (Case 2)	5 mo.	F	+	+	0	+	+	
Rogers and Edwards (Case 3)	2.5 mo.	F	0	+	+	0	+	Absence of lower limbus of fossa ovalis; patent foramen ovale
Rogers and Edwards (Case 4)	6 mo.	F	+	+	+	+	+	Widely patent foramen ovale
Rogers and Edwards (Case 5)	36 yr.	M	0	+	+	0	+	Subacute bacterial endocarditis on left side
Rokitansky[10] (Case 1112)	12 days	M	–	–	–	–	+	
Rokitansky[10] (Case 2303)	Stillborn	M	–	0	–	–	+	Defect in membranous septum; infantile coarctation of aorta
Rokitansky[10] (Case 3200)	Newborn	—	–	+	–	–	0	Defect in membranous septum; persistent truncus arteriosus
Rokitansky[10] (Case 3178)	2 days	F	–	+	–	–	0	Situs inversus of heart and liver
Rokitansky[10] (Case 2071)	Middle age	M	–	+	–	–	+	
Rokitansky[10] (Case 3153)	23 yr.	F	–	+	–	–	0	
Rokitansky[10] (Case 264)	19 yr.	M	–	+	–	–	0	
Rokitansky[10] (Case 1882)	22 yr.	M	–	+	–	–	0	
Rokitansky[10] (Case 2226)	60 yr.	F	–	+	–	–	0	
Rudolph (Quoted by Söldner[36])	23 yr.	M	–	+	–	–	0	Bacterial endocarditis
Rudolph (Quoted by Söldner[36])	8 yr.	F	–	+	–	–	0	Patent ductus arteriosus
Schleussing[37] (Case 5)	9.5 mo.	M	+	+	–	–	0	
Schleussing[37] (Case 6)	7 days	F	–	+	–	–	0	
Schmincke and Doerr[38]	2 mo.	F	–	+	–	+	+	Bulboventricular version; corrected transposition of great vessels
Seham[39] (Case 6)	15 mo.	M	+	+	+	0	0	
Sternberg[40]	16 yr.	M	–	+	–	+	+	
Terplan and Sanes[41]	24 days	F	+	0	+	+	0	
Theremin[42]	—	—	–	+	–	–	+	Patent ductus arteriosus
Turner[43]	14 mo.	—	–	+	–	–	0	Persistent left superior vena cava

*Including five cases reported in this paper.

Key to Table I: + Present.
0 Absent.
– Data not available.

Concerning two cases of Hart,[23] Gunn and Dieckmann[3] accepted one case and rejected the other one, which they thought should be classified as a case of cor triloculare biventriculare. We agree with that interpretation. We are including Hart's Case 12 and rejecting his Case 13.

In reviewing the other articles quoted by Robinson,[35] we found only one (Case 69) instead of three cases said to have been reported by Leech,[26] and two instead of five cases said to have been reported by Gibson and Clifton.[46] As indicated previously, we are not including these two cases in Table I. The case of Lightner[52] should be classified as a case of cor biloculare. Decision concerning the case of Morgan and Sprenkel,[53] in which the patient was a woman 61 years of age, is difficult to make from the description and photographs, but it probably should be classified as a case of cor triloculare biventriculare. The cases of Goetsch,[22] Ash, Wolman, and Bromer,[18] Meeker,[27] Robson,[7] Mönckeberg[29] (1924), and Robinson's own case are acceptable as examples of persistent common atrioventricular canal. Concerning the 1923 paper of Mönckeberg[28] on the subject under consideration, Robson accepted but one case therein. We feel that the second specimen described by Mönckeberg,[28] namely, that of a heart from the museum of Bonn Institute dated 1884, should be accepted as an example of the anomaly under consideration.

In reviewing the cases listed in Table I, we found that persistent common atrioventricular canal is usually, but not always responsible for the death of the patient at an early age. The oldest patient in the group was the 61 year-old woman in von Rokitansky's Case 2226. In this case, the defect did not include a deficiency of the interventricular septum. This is an unusual case since most persons who have the lesion under consideration die at an early age. In Table II are listed the ages of the patients at the time of death in the forty-eight recorded cases in which the age was stated and in our five cases. About one-fifth of the patients died before the age of 1 month, and more than half of the patients died before they were 1 year of age. Only five of the fifty-three patients lived beyond the age of 30 years. The median age at the time of death in these cases was

TABLE II. AGE OF PATIENTS AT TIME OF DEATH

AGE	PATIENTS	
	NUMBER	PER CENT
Less than 1 mo.	11	20.8
1-11 mo.	16	30.2
12-23 mo.	10	18.9
2- 4 yr.	2	3.8
5- 9 yr.	1	1.9
10-19 yr.	4	7.5
20-29 yr.	4	7.5
More than 30 yr.	5	9.4
Total	53*	100.0

*Data not available in two cases.

10 months. There was no significant predilection for one sex. In the forty-five cases in which data on sex were available, twenty-five of the patients were male and twenty were female.

Cardiac enlargement was a common manifestation both clinically and pathologically. In the collected series, there were forty-five cases in which the size of the heart was recorded. Forty-one hearts showed enlargement and four were considered to be of normal size. When cardiac enlargement was present, right ventricular hypertrophy and right atrial dilatation were the usual features. The explanation for these changes may be found in the abnormal circulation caused by the defect. Briefly reiterated, a right-sided arteriovenous shunt is in operation. In many of the reported cases, the orifice of the pulmonary valve and the pulmonary artery were dilated and at times the aortic orifice was narrow. This feature was stressed by Sternberg[40] in 1913. These alterations should not be considered developmental defects since they are the result of greater blood flow than through the right circuit.

Persistent common atrioventricular canal may be associated with true major developmental anomalies of the heart. Indeed, Keith[25] expressed the opinion that that association always existed. In reviewing the two illustrations on persistent common atrioventricular ostium in Keith's article, however, Gunn and Dieckmann[3] and we were unable to recognize an associated anomaly. Moreover, cases of persistent common atrioventricular canal without associated major cardiac anomalies have been reported prior to the publication of Keith's article and afterward. It is evident, therefore, that in certain hearts, persistence of the common atrioventricular canal with patent interatrial foramen primum may be the only anomaly found. Significant major anomalies of the heart or great vessels were present in only twelve of the fifty-five cases. The types of the associated major cardiac anomalies are recorded in Table I. It appears that these do not fall into any specific type, with the exception of the absence of cor biloculare or cor triloculare. Persistence of the common atrioventricular canal is a constant feature in cases of cor biloculare and in many cases of cor triloculare. In hearts in which there is failure of formation of four cardiac chambers, persistence of the common atrioventricular ostium (when it does occur, and it frequently does) should be considered an incidental manifestation of a more serious defect. In the interest of accurate classification of congenital cardiac disease, hearts which have two or three chambers and a common atrioventricular canal should be classified on the basis of the more serious defect of which persistent common atrioventricular canal is merely an integral part. These anomalies should be segregated from those in which persistence of the common atrioventricular canal is the major and essential defect.

By following this rule, we have eliminated certain cases which were reported as examples of persistent common atrioventricular ostium. In our own collection of hearts, we have a specimen from a newborn monster in which the region of the atrioventricular valve is identical to that in our Case 1. This specimen shows complete absence of the upper interatrial septum, the only vestige of an interatrial septum being a sickle-shaped cord running between the anterior and

posterior atrial walls over a common atrioventricular canal and valve. In this specimen, we feel that the virtual absence of the interatrial septum justifies classifying the anomaly as cor triloculare biventriculare.

Reference to Table I reveals that cyanosis was observed in twenty-three cases. It was absent in seven cases and in the remaining twenty-five cases, no reference was made to this sign. In some cases, cyanosis was present at birth; in others, it developed later in life. Once apparent, cyanosis may have been constant or intermittent, as during crying. In the case of Abbott and Kaufmann,[16] there evidently was no cyanosis at any time. The patient died of a ruptured appendix at 36 years of age. From our interpretation of the left-to-right direction of blood flow through the defect in the compensated heart, cyanosis would not be expected. Only after there is cardiac failure or pulmonary complications does cyanosis appear. Using a functional classification, persistent common atrioventricular canal with patent interatrial foramen primum may be included in the cyanose tardive group.

In Table I, we have listed the occurrence of cardiac murmurs. In very few of the reported cases were the murmurs described in any detail. When present, they were usually classified as systolic. A murmur was recorded in twenty-two of the twenty-five cases in which an adequate history was given with reference to this sign.

That congenital cardiac disease often accompanies mongolism is well recognized. Abbott[14] said that, according to Thomson, one of six Mongolian idiots had congenital cardiac disease. In addition, she said that von Hofe found anomalous hearts in fourteen, or 9.9 per cent, of 150 Mongolian idiots. Benda[54] said that cardiac anomalies are present in 75 per cent of cases in which children who have mongolism die in the first two years of life and that congenital cardiac malformations are present in 35 per cent of cases in which such children live more than two years.

Abbott[14] indicated that the lesion under consideration is the usual one in cases in which mongolism is associated with congenital cardiac disease. She said that in three of seventeen cases in which mongolism was associated with congenital cardiac disease, examination revealed "that curious combination of a defect of the lower part of the interauricular septum (persistent ostium primum) or a persistent ostium atrioventriculare commune that has already been commented upon by the writer and others as being the usual form of cardiac defect met with in Mongolian idiocy."

From the reviews of a number of authors, it is evident that Abbott's view may have been somewhat too rigid. Philpott,[45] who reported eighty cases of anomalies of the heart or great vessels, found but one case of persistent common atrioventricular ostium, yet in seven of the eighty cases the patients were Mongolian idiots. Gibson and Clifton[46] found two examples of the lesion which forms the subject of this paper in a group of 105 hearts of infants or older children with congenital cardiac disease. Each of the two patients were Mongolian idiots; however, there were five other Mongolian idiots with different major anomalies of the heart or great vessels. It appears that in a group of Mongolian

idiots with congenital cardiac disease any of the known types of cardiac anomalies may be encountered.

On the other hand, there is a decided tendency for mongolism to be associated in persistent common atrioventricular ostium. Of the fifty-five cases which we are reviewing, mongolism was recorded in seventeen cases and its absence was recorded or can be assumed in eight cases. In the remaining thirty cases, the history was inadequate with respect to this condition. The frequent association of mongolism with persistent common atrioventricular canal is supported by three of our five cases. To attempt an explanation for this association on the basis of our present knowledge leads us only into the field of time-consuming and purposeless speculation.

The complication of subacute bacterial endocarditis in congenital cardiac disease is well known, yet it is not common in cases of persistent common atrioventricular ostium. In 1938, Goetsch[22] reported a case in which staphylococcic subacute bacterial endocarditis developed on the valve of the persistent common atrioventricular ostium. The patient was a girl, aged 18 months. Goetsch was unable to find a report of a similar case in the literature. We feel that a case reported by Rudolph, quoted by Söldner,[36] in which the patient was a 23-year-old man, should be added to that of Goetsch, as should our Case 5. Goetsch's explanation for the infrequent occurrence of subacute bacterial endocarditis in association with persistent common atrioventricular ostium was that the patients usually died at an early age, thereby making less likely the chances for the development of this complication. This explanation seems entirely plausible.

To make with certainty the exact clinical diagnosis of persistent common atrioventricular ostium is difficult according to present standards for the differential diagnosis of congenital cardiac disease. In childhood, the occurrence of acquired cyanosis, especially intermittent cyanosis with crying, enlargement of the right side of the heart, a systolic murmur, and mongolism might suggest the diagnosis. In cases in which the patients are adults, a history of late development of cyanosis together with enlargement of the right side of the heart might suggest the diagnosis, but it would be difficult to distinguish clinically persistent atrioventricular canal with persistent foramen primum from simple interatrial septal defect.

SUMMARY

This paper is based on a report of five cases* of the congenital cardiac disease termed incomplete division of the atrioventricular canal with patent interatrial foramen primum (persistent common atrioventricular ostium) and on a review of the essential pathologic and clinical features in an additional fifty cases reported in the literature. In the entire group of fifty-five cases, the median age

*Since the time of preparation of the manuscript of this paper, we have observed a sixth example. The anomaly was found in a stillborn full-term female fetus. Both the septal leaflet of the tricuspid valve and aortic leaflet of the mitral valve were cleft, and a common atrioventricular valve was present. There was patency of the interatrial foramen primum and a defect in the posterior portion of the interventricular septum. In this connection, the atrioventricular junction was virtually identical to that in Cases 1, 2, and 3. There was also an anatomic patency of the foramen ovale.

of the patients at the time of death was 10 months. More than half of the patients died before they were 1 year of age. Only five of the patients lived beyond the age of 30 years. The anomaly apparently does not have any predilection for either sex.

In the fifty-five cases, it appears that the lesion under consideration acts essentially as does a simple interatrial septal defect. Enlargement of the right side of the heart and widening of the pulmonary artery orifice are common associated secondary lesions. Cyanosis may be present at birth, but is usually acquired. When this manifestation develops, it is a sign of failure of the right side of the heart, pulmonary disease, or both. Cardiac murmurs, usually systolic, are frequently observed; they occurred in twenty-two of twenty-five cases in which an adequate history was given with reference to this sign.

Monogolism is a relatively common associated finding in cases of incomplete division of the atrioventricular canal with patent interatrial foramen primum. In those case reports in which there was an adequate history, mongolism was recorded as having been present in seventeen cases and its absence was recorded or could be assumed in eight cases.

Bacterial endocarditis was observed in three of the fifty-five cases.

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INTERPRETATION OF THE ELECTROCARDIOGRAM IN DEXTROCARDIA WITH SITUS INVERSUS

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WALLER,[1] in 1889, was the first to present the electrocardiographic findings in dextrocardia with situs inversus. He showed that the usual electrical relationships were reversed, in that it was necessary to invert Lead I and interchange Leads II and III to obtain a record like that from a normally placed heart. Many papers have been presented since that time verifying and amplifying Waller's original report. Many of the reports relate to the incidence of dextrocardia with and without other abnormalities. Most of these reports merely state that it is or is not typical of dextrocardia with situs inversus and show the confusion which has arisen in the interpretations of these electrocardiograms when other electrocardiographic abnormalities are present.

In 1911, Owen[2] reported a case of a 28-year-old woman with dextrocardia with situs inversus and with mitral stenosis. He included the electrocardiographic findings of the three standard limb leads, which he transposed as suggested by Waller. His electrocardiographic interpretation is open to question because of confusion in terminology.

Potts and Ashman,[3] in 1926, presented a case of dextrocardia with situs inversus and a marked "functional" left axis deviation, but without other comment or interpretation. Willius[4] presented a similar case with known hypertension in which the T wave in Lead I was upright instead of negative as would be expected in uncomplicated dextrocardia, stating that it corresponded to the negative T_1 commonly seen with hypertension in normally placed hearts. Smith and Horton[5] described a case of dextrocardia and showed, in their patient, that a normal record could be obtained by inverting Lead I and interchanging Leads II and III. Crawford and Warren[6] reported the case of a 58-year-old man with dextrocardia and right-sided precordial pain radiating to the right arm. The electrocardiogram, after reversing the leads, showed a negative and coved T_2 and T_3 consistent with the diagnosis of coronary occlusion involving the posterior basal region of the left ventricle. Manchester and White[7] reported a case of dextrocardia with hypertension and coronary artery disease. They, like

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Crawford and Warren, reversed the leads and obtained a negative and coved T_1, and T_4, which were interpreted as being due to hypertension and coronary artery disease. Lys[8] reported the case of a 23-year-old girl with dextrocardia, complete heart block, and clinical evidence of a patent interventricular septum.

Because of the confusion attendant on the study of the electrocardiograms reproduced in these reports, it seemed opportune to review the problem of electrocardiographic interpretation in cases of dextrocardia with situs inversus, and to attempt to enhance the value of the electrocardiogram in these cases.

MATERIAL

Our attention was directed to this problem by the electrocardiographic findings in a patient with dextrocardia, situs inversus, hypertension, coronary artery disease, and probable subdeltoid bursitis. This led us to restudy the electrocardiograms in twelve other patients on whom electrocardiograms had been taken from 1932 to 1946; six of these returned to the hospital for additional observations. In all cases, the diagnosis of situs inversus was established by x-ray examination of the chest, and in most cases, by x-ray examination of the gastrointestinal tract including the large bowel, or by laparotomy. The age of the patients varied from 6 to 70 years. In this paper, discussion will be limited to cases of dextrocardia with situs inversus and will not include cases of isolated dextrocardia (that is, without situs inversus), since in the latter condition no generalizations as to electrocardiographic interpretation can be made.

METHODS

In each of the seven cases which we were able to study intensively, a history was taken and physical examination was done, followed by an x-ray examination of the chest and an electrocardiogram. The three standard limb leads of the electrocardiogram were taken in the usual manner: that is, Lead I, right arm to left arm; Lead II, right arm to left leg; and Lead III, left arm to left leg. Ten precordial leads were taken with the precordial electrode placed as follows (Fig. 1): In Lead $CF_1(L)$ the exploring electrode was placed in the fourth intercostal space to the left of the sternum; in Lead $CF_2(R)$, in the fourth intercostal space to the right of the sternum; in $CF_3(R)$, midway between $CF_2(R)$ and $CF_4(R)$; in $CF_4(R)$, fifth intercostal space in the right mid-clavicular line; in $CF_5(R)$, fifth intercostal space in the right anterior axillary line; $CF_6(R)$, fifth intercostal space in the right mid-axillary line; $CF_3(L)$, midway between $CF_1(L)$ and $CF_4(L)$; $CF_4(L)$, fifth intercostal space in the left mid-clavicular line; $CF_5(L)$, fifth intercostal space in the left anterior axillary line; and $CF_6(L)$, fifth intercostal space in left mid-axillary line; the indifferent electrode was attached to the left leg.

It became apparent on studying the electrocardiograms that conventional terminology was confusing. This was the case, not only in the interpretations of the electrocardiograms in dextrocardia, but also in attempting to understand what other authors had written about the subject. This led us to devise a means

of analysis which would be less confusing than that now in use. Situs inversus is a mirror-image phenomenon, a view supported by both anatomic and electrocardiographic evidence.[9,10] We, accordingly, inverted Lead I and interchanged Leads II and III before attempting to interpret the electrocardiogram, thus

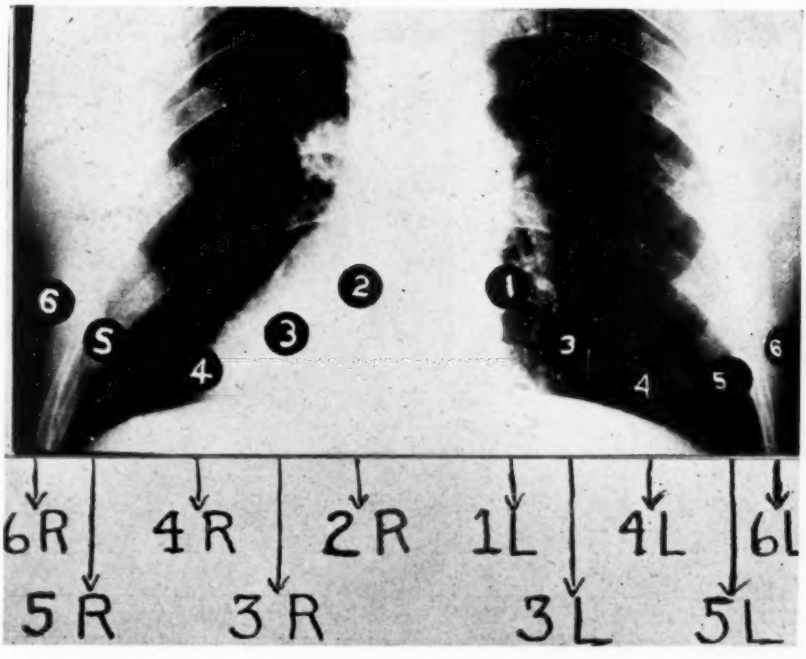

Fig. 1.—In this figure is reproduced the x-ray photograph of the chest of R. K. (Case 1), showing dextrocardia with slight enlargement of the systemic ventricle and a slight increase in lung markings. Superimposed on the reproduction of the x-ray film are numbers denoting the sites of derivation of the multiple precordial leads.

making it a record similar in all respects to that of a patient with a normally placed heart (Fig. 2). It was then decided to omit all reference to right and left ventricle, as well as to right axis deviation and left axis deviation, because "left" is so indelibly associated with that ventricle which pumps systemic blood, and "right" with that ventricle which pumps pulmonary blood. In place of these conventional terms we have used the terms "systemic" ventricle, applying to that ventricle which pumps blood to the systemic circulation, and "pulmonic" ventricle, applying to that ventricle which pumps blood to the pulmonary circulation. We then take the logical course of using the terms systemic axis deviation and pulmonic axis deviation. It thus becomes possible to interpret the electrocardiograms in terms of axis deviation and ventricular hypertrophy without confusion. When this is done, the RS-T deviations from normal are subject to interpretation in the same manner as in electrocardiograms derived from normally placed hearts.

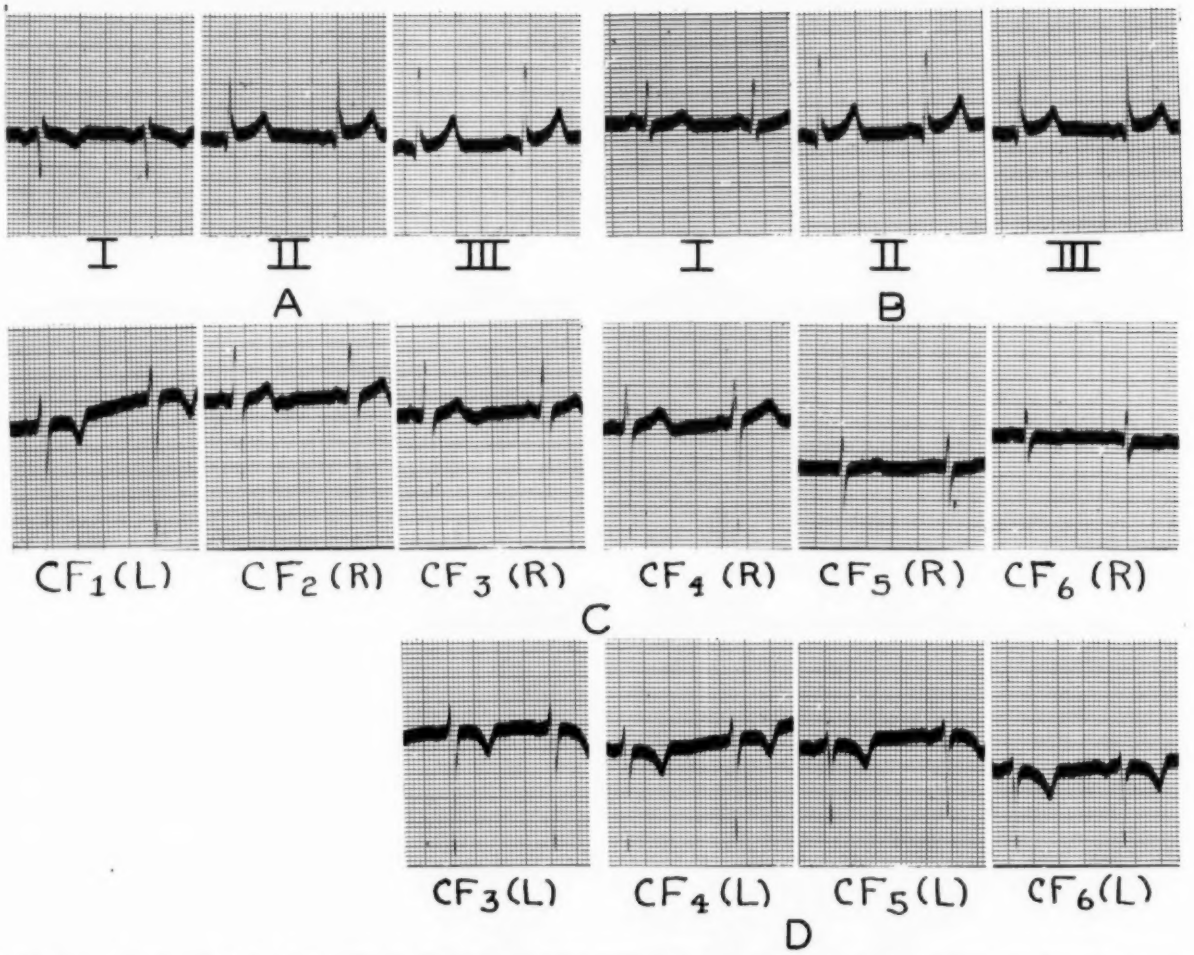

Fig. 2.—In this figure are reprinted the electrocardiograms derived from Patient E. S. (Case 5). In this figure and Figs. 3 to 7 inclusive, the standardization is such that one millivolt produced 1.0 cm. deflection of the string. Divisions of the ordinates equal 10^{-4} volts. Divisions of the abscissae equal 0.04 second. The tracings in this figure represent the findings from a patient with dextrocardia without signs or symptoms of heart disease and in whom the electrocardiogram is essentially normal. Fig. 2,*A* shows the three standard limb leads of the electrocardiogram as they were taken. Fig. 2,*B* shows the electrocardiogram printed with Lead I upside down and Leads II and III interchanged. Fig. 2,*C* shows the six precordial leads, $CF_1(L)$ to $CF_6(R)$ inclusive, taken from the left border of the sternum across the right side of the chest as shown in Fig. 1. Fig. 2,*D* shows the four precordial leads, $CF_3(L)$ to $CF_6(L)$ inclusive, taken from the left side of the chest as shown in Fig. 1.

The ten multiple chest leads were interpreted in the conventional manner, as the position of the precordial electrode for the various leads had the same relation to the position of the heart in the chest as is customary in the patient with a normally placed heart.

The electrocardiograms of the six patients who were unable to return for additional study were interpreted according to the technique which has been described. In none of these cases, however, had chest leads been taken.

CASE REPORTS

CASE 1.—R. K. No. 448306, a 56-year-old carpenter, was admitted to the private service with the chief complaint of pain in both shoulders for six months.* He had known of the dextrocardia since early childhood. He had consumed large amounts of alcohol for many years, until a large gastrointestinal hemorrhage one and one-half years before admission had caused him to stop. He had suffered from sinus infection for many years, and nasal polyps had been removed on several occasions. There was no history of chronic cough. He had known that he had hypertension with a systolic level around 180 mm. Hg for many years. There was no history of cardiac or respiratory distress. On physical examination, the pulse rate was 84 per minute, the respiratory rate was 16 per minute, and the blood pressure, 194/94. There were bilateral nasal polyps. There was a dextrocardia with slight enlargement to the right on percussion. A loud, harsh systolic murmur was heard at the apex, but could also be heard over the entire precordium. Normal sinus rhythm was present. The liver was palpable 2.0 cm. below the left costal margin. X-ray examination of the sinuses showed pansinusitis. X-ray examination of the chest showed dextrocardia with slight enlargement of the systemic ventricle and slight fibrosis of the lungs. The gastrointestinal x-ray series showed a situs inversus without other abnormalities. X-ray examination of the shoulder regions showed minimal osteoarthritis.

The electrocardiogram (Fig. 3) showed systemic axis deviation and negativity and coving of T_1 and of the T waves in Leads CF_2(R), CF_3(R), and CF_4(R) from the right side of the chest, with depression of the RS-T segments in Leads I and II, and in Leads CF_3(R), CF_4(R), CF_5(R), and CF_6(R) (from the right side of the chest). The T waves of Leads CF_3(L), CF_4(L), CF_5(L), and CF_6(L) (from the left side of the chest) were all upright, and the corresponding RS-T segments were elevated. The changes were considered consistent with systemic ventricular hypertrophy due to the hypertension, and with arteriosclerotic coronary artery disease.

CASE 2.—M. R. (No. 17300), a 37-year-old printer, was first admitted to the hospital at the age of 24 years with the complaint of recurrent left lower abdominal pain. Physical examination and x-ray examination of the chest showed a dextrocardia with situs inversus. One brother was also known to have dextrocardia. A soft apical systolic murmur was described. A laparotomy was performed through a left rectus incision and a scarred, fibrosed appendix in the left lower quadrant was excised. In the three standard leads of the electrocardiogram (Fig. 4) taken at that time, there was no deviation of the electrical axis, but T_1 was negative and coved.

Thirteen years later, this patient returned at our request for further study. He had continued to have recurrent attacks of abdominal pain for which he had had further abdominal operations without relief. He now had a ventral hernia. He had no cardiac or respiratory complaints. On physical examination, he was moderately obese. The pulse rate was 75 per minute; respiratory rate, 20 per minute; and the blood pressure, 176/96. This fell to 136/88 on later observations. The heart was slightly enlarged to the right, the sounds were of good quality, and no murmurs were heard. The lungs were clear. X-ray examination of the chest showed dextrocardia without other abnormalities. The electrocardiogram (Fig. 5) showed a systemic axis deviation which had not been present thirteen years before, and only slight changes in the T waves and RS-T segments had taken place on comparison of the two records. The multiple chest leads showed that all

*We take this opportunity to thank Dr. Henry A. Cromwell for permission to study and report the data relating to this patient.

CF6(L) inclusive, taken from the left side of the chest as shown in Fig. 1. *Fig. 2,D* shows the four precordial leads, CF_3(L) to CF_6(L) inclusive, taken from the right side of the chest as shown in Fig. 1.

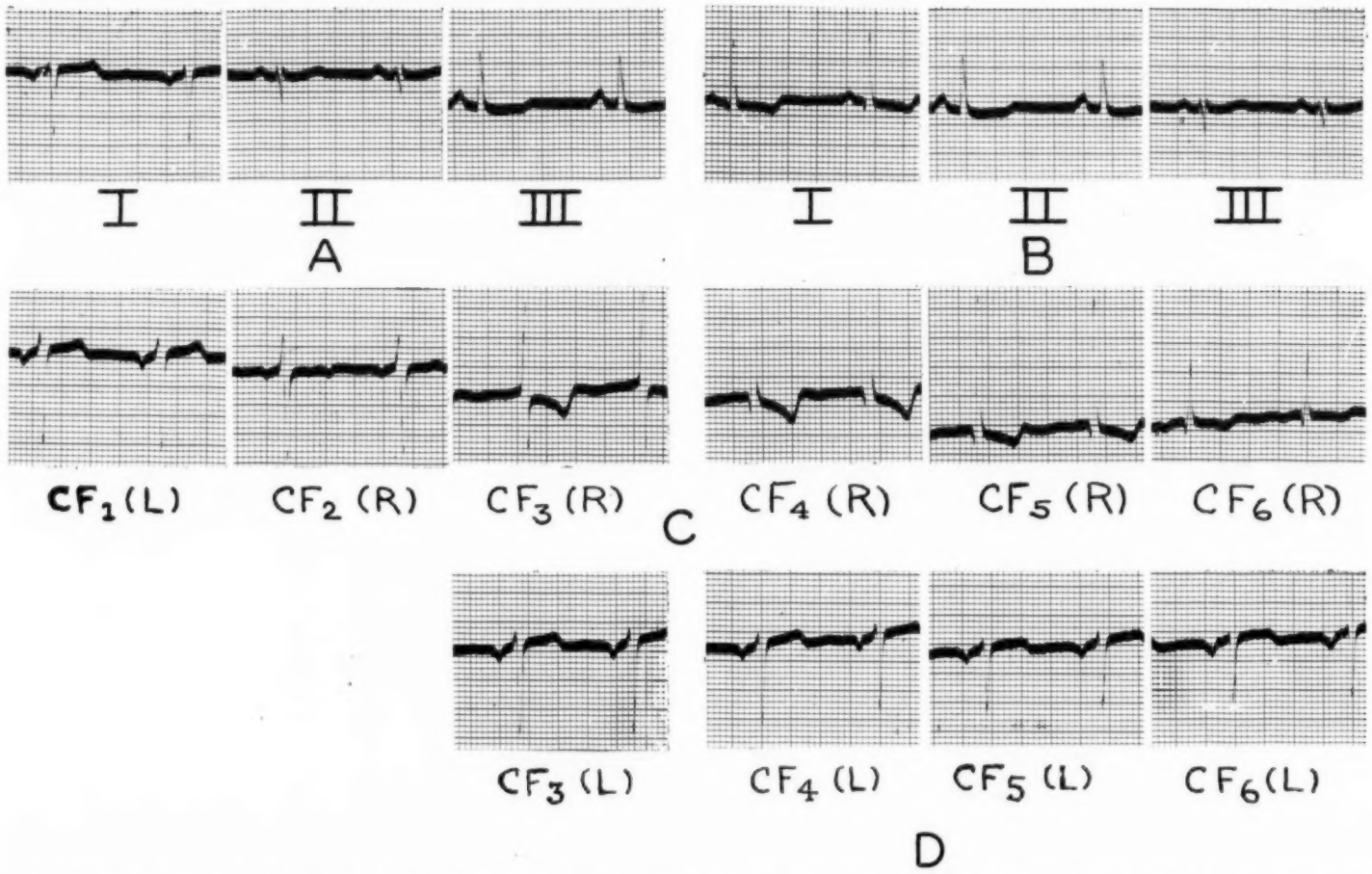

Fig. 3.—In this figure are reprinted the electrocardiograms from Patient R. K. (Case 1), showing systemic axis deviation and RS-T deviations from normal seen with hypertension and coronary artery disease. Fig. 3,*A* shows the three standard limb leads of the electrocardiogram as they were taken. Fig. 3,*B* shows the electrocardiogram with Lead I printed upside down and Leads II and III interchanged. Fig. 3,*C* shows the six precordial leads, $CF_1(L)$ to $CF_6(R)$ inclusive, taken from the left border of the sternum across the right side of the chest as shown in Fig. 1. Fig. 3,*D* shows the four precordial leads, $CF_3(L)$ to $CF_6(L)$ inclusive, from the left side of the chest as shown in Fig. 1.

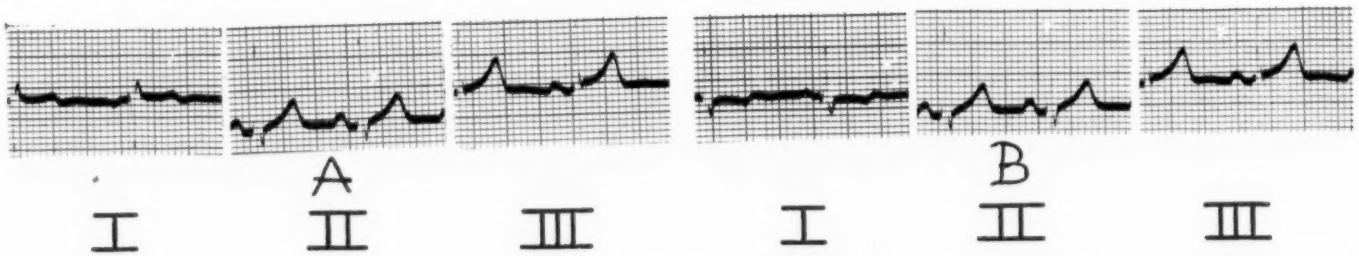

Fig. 4.—In this figure is reprinted the electrocardiogram from M. R. (Case 2), taken Dec. 23, 1932. Fig. 4,*A* shows the three standard limb leads as they were taken. Fig. 4,*B* shows the three standard limb leads with Lead I upside down, and Leads II and III interchanged.

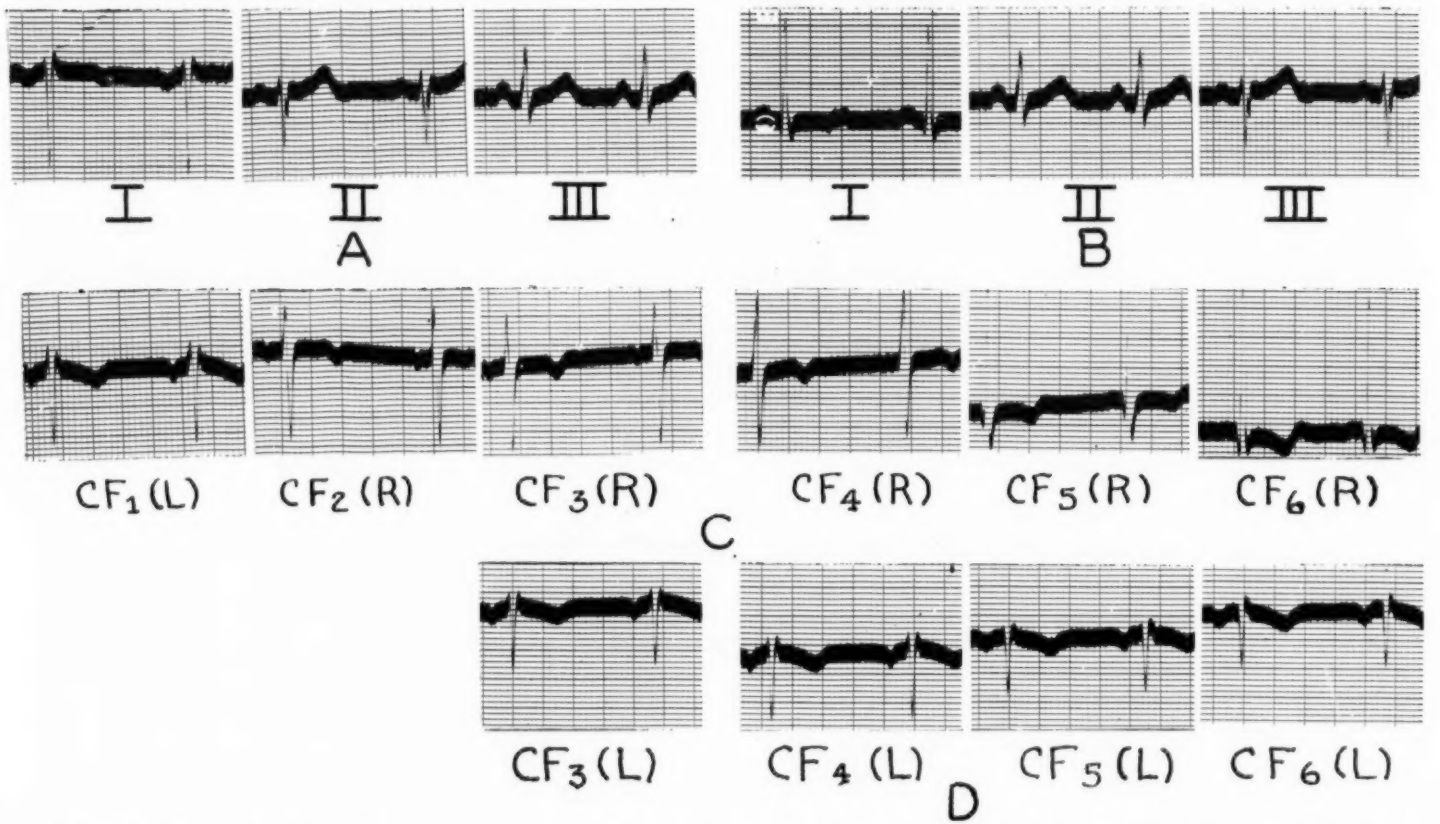

Fig. 5.—In this figure are reprinted electrocardiograms from M. R. (Case 2), taken Sept. 7, 1946. Fig. 5,*A* shows the three standard limb leads as they were taken. Fig. 5,*B* shows the three standard limb leads with Lead I upside down and Leads II and III interchanged. Fig. 5,*C* shows the precordial leads, $CF_1(L)$ to $CF_6(R)$ inclusive, taken from the left border of the sternum across the right side of the chest. Fig. 5,*D* shows the precordial leads, $CF_3(L)$ to $CF_6(L)$ inclusive, taken from the left side of the chest.

T waves were negative and coved. The negative T waves from the right side of the chest were considered abnormal, but this configuration in leads from the left side of the chest is probably normal. Four months later, the electrocardiogram (Fig. 6) was repeated with ten precordial leads. At this time he was completely asymptomatic with regard to his cardiorespiratory and gastrointestinal systems, and the electrocardiogram was normal except for systemic axis deviation. T_1 was upright as were the T waves in the chest leads taken from the right side of the chest, those in the leads taken from the left side of the chest remaining negative and coved. An exercise tolerance test and an anoxemia test showed no abnormal findings.

The exercise tolerance test was done as follows: After a control resting electrocardiogram with chest lead was taken, the patient walked up and down over a stair-step designed for this test until subjective complaints such as dyspnea or precordial pain developed, or until it became apparent after many turns on the stair-steps that no subjective complaints would develop. An electrocardiogram was taken immediately on cessation of exercise, and again after fifteen minutes of rest. The changes in the T waves and RS-T segments were measured in the three records and significant changes were recorded.

The anoxemia test was done as follows: The patient rested for one-half hour under basal conditions. The mask was then adjusted to fit. A control electrocardiogram was taken during the breathing of atmospheric air, and then repeated every five minutes during the breathing of a 10 per cent oxygen and 90 per cent nitrogen mixture. This was continued until the patient complained of pain, or for twenty minutes, at which point atmospheric air was again breathed through the mask. The electrocardiogram was repeated one minute later and at five-minute intervals for ten minutes. Significant changes in the T waves and RS-T segments in the serial electrocardiograms were recorded, using the criteria established by Levy.

CASE 3.—M. M. (No. 24369), a 45-year-old housewife, first came to the hospital at the age of 31 years, complaining of frequency of urination. At that time, a dextrocardia was discovered. No other abnormalities were found on physical examination. The blood pressure was 128/80. An electrocardiogram was not taken at that time. From the age of 39 to the age of 44 years she was seen intermittently in the clinic for a duodenal ulcer, which led to a subtotal gastrectomy for massive hemorrhage at the age of 44 years. A gastrointestinal x-ray series, a barium enema, and the laparotomy confirmed the presence of situs inversus. X-ray examination of the chest showed the dextrocardia with slight enlargement of the systemic ventricle. The blood pressure varied from 140/85 to 150/110. One year later, this patient was asymptomatic, and there were no complaints referable to the cardiorespiratory system. The blood pressure was 140/90. Physical examination revealed the dextrocardia without enlargement of the heart to percussion, a normal sinus rhythm was present, and no murmurs were heard. An x-ray examination of the chest showed no changes from the previous examination.

The electrocardiogram showed systemic axis deviation. The T waves in the three limb leads were normal. In the ten precordial leads the T waves were negative and coved in CF_3(L), CF_4(L), CF_5(L), and CF_6(L) (from the left side of the chest), and in CF_2(R), CF_3(R), and CF_4(R) (from the right side of the chest). In Leads CF_5(R) and CF_6(R) (from the right side of the chest) the T waves were upright. The negativity and coving of the T waves in Leads CF_3(R) and CF_4(R) (from the right side of the chest) were considered abnormal and attributed to the systemic axis deviation, there being no clinical evidence of coronary artery disease.

CASE 4.—E. R. (No. 448231), a 39-year-old housewife, came to the lying-in clinic for prenatal care. A dextrocardia and a twenty-four-week intra-uterine pregnancy were found. The blood pressure was 130/90. There was no enlargement of the heart to percussion, a normal sinus rhythm was present, and no murmurs were heard. An x-ray examination of the chest showed a dextrocardia without other abnormalities. The electrocardiogram, including the ten precordial leads, showed no abnormalities except low amplitude of QRS_3, suggesting a beginning systemic axis deviation. The T waves in the leads taken from the left side of the chest were negative and coved; those from the right side of the chest were upright.

At term a mild pre-eclampsia developed, the blood pressure rising to 170/110. A spontaneous delivery occurred, the blood pressure falling, post partum, to 140/90. Three months later, the blood pressure had again risen to 170/100, but no complaints were recorded at that time. Four

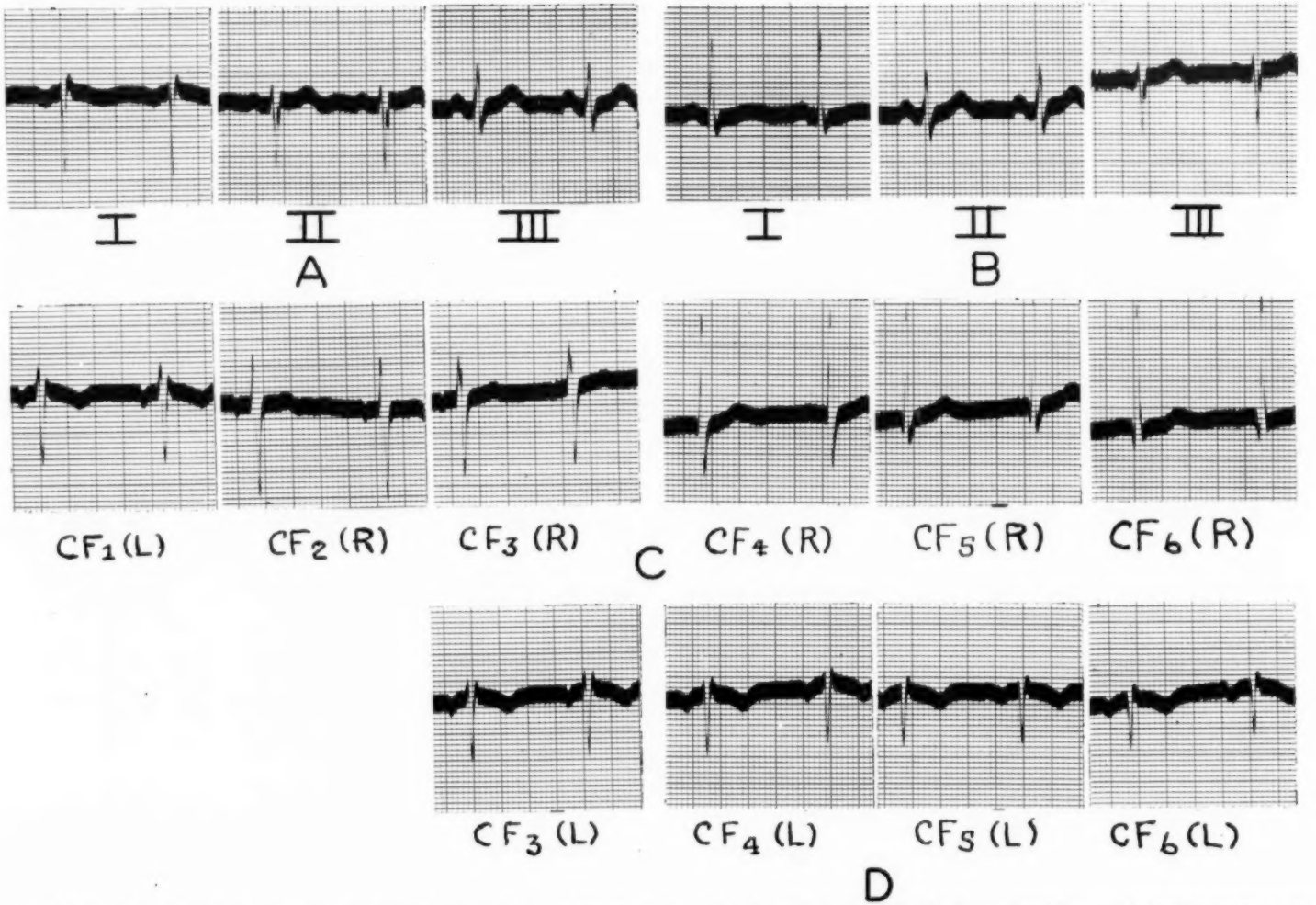

Fig. 6.—In this figure are reprinted electrocardiograms from M. R. (Case 2), taken Jan. 30, 1947. Fig. 6,*A* shows the three standard limb leads as they were taken. Fig. 6,*B* shows the three standard limb leads with Lead I upside down and Leads II and III interchanged. Fig. 6,*C* shows the precordial leads, $CF_1(L)$ to $CF_6(R)$ inclusive, taken from the left border of the sternum across the right side of the chest. Fig. 6,*D* shows the precordial leads, $CF_3(L)$ to $CF_6(L)$ inclusive, taken from the left side of the chest.

and one-half months post partum the blood pressure was 135/85, and the patient complained of mild precordial pulling sensation on exertion associated with heaviness in the right arm. An electrocardiogram at this time, with the ten precordial leads, showed that QRS_3 was no longer of low amplitude; there were no other significant changes from the previous record. During an exercise tolerance test she complained of precordial pulling, heaviness in the right arm, and dyspnea, but there were no significant changes in the electrocardiogram. An anoxemia test likewise induced no significant changes in the electrocardiogram.

CASE 5.—M. V. (No. 44984), a 25-year-old unemployed man, was first seen in the pediatric clinic at the age of 12 years, complaining of frequent colds. The physical examination was negative except for a dextrocardia, and a short rough systolic murmur best heard at the apex. An x-ray examination of the chest confirmed the dextrocardia, but was otherwise normal. The electrocardiogram at that time showed no axis deviation. The RS-T segments in Leads II and III were elevated 1.0 mm., but there was no abnormality in the configuration of the T waves. No chest leads were taken.

He was followed in subsequent years in the ear, nose, and throat and pulmonary clinics for sinusitis and intermittent cough. X-ray examinations of his chest were negative. At the age of 21 years he entered the U. S. Army and served for three years; at no time did he have complaints referable to his cardiorespiratory system. At the age of 25 years, at the time of our examination, he had no complaints referable to the heart or respiratory system. An x-ray examination of the chest was negative except for the dextrocardia. The blood pressure was 140/90. The heart was not enlarged, the sounds were of good quality, and no murmurs were heard. The electrocardiogram (Fig. 2) showed no changes in the three limb leads, the RS-T segments in Leads II and III remaining elevated as they had been thirteen years previously; the ten precordial leads showed no abnormalities. The T waves in leads taken from the right side of the chest were upright, and in leads from the left side of the chest the T waves were negative and coved.

CASE 6.—I. C. (No. 156909), an 11-year-old school girl, had been followed in the pediatric clinic since the age of 2 years for erythroblastic (Cooley's) anemia. She had received blood transfusions at frequent intervals to maintain her blood count at adequate levels. Physical examination revealed dextrocardia. At the age of 4 years she underwent a splenectomy, the spleen being removed from the right side of the abdomen, but there was no improvement in the anemia. At the age of 11 years, at the time of our examination, physical examination revealed her blood pressure to be 112/58. The heart was slightly enlarged to the right, the sounds were of good quality; the second pulmonic sound, heard in the right second intercostal space, was greater than the second aortic sound. No murmurs were heard. An x-ray examination of the chest showed dextrocardia with slight enlargement of the systemic ventricle, a finding which had been present on previous x-ray films of the chest. The electrocardiogram showed a low amplitude of QRS_3, but was otherwise entirely normal. Of the ten precordial leads, those taken from the left side of the chest showed negativity and coving of the T waves, and those taken from the right side of the chest showed upright T waves.

CASE 7.—M. C. (No. 274598), a 6-year-old school girl, was found to have dextrocardia with situs inversus at the time of her birth. She had no complaints referable to her cardiorespiratory system. The physical examination was negative except for the dextrocardia. The heart was not enlarged, the sounds were of good quality; the second pulmonic sound, heard in the right second intercostal space, was greater than the second aortic sound. No murmurs were heard. An x-ray examination of the chest was negative except for dextrocardia. The electrocardiogram, including the ten precordial leads, showed no axis deviation, and no abnormalities were noted. The T waves of the chest leads derived from the left side of the chest and of $CF_2(R)$, from the right side of the chest, were negative and coved; the T waves of Leads $CF_3(R)$, $CF_4(R)$, $CF_5(R)$, and $CF_6(R)$ (from the right side of the chest) were upright.

CASE 8.—R. S. (No. 79982), a 40-year-old unemployed man, was admitted to the medical service in 1934, and discharged with a diagnosis of idiopathic convulsions. He gave a history of chronic postnasal drip, but no significant findings referable to his cardiorespiratory system. Physical examination revealed dextrocardia, which was confirmed by x-ray examination of the

chest and by a gastrointestinal x-ray series. The blood pressure was 118/76. No cardiac abnormalities were noted, other than the dextrocardia. The electrocardiogram showed a systemic axis deviation and a low amplitude of the T wave in Lead I. This last finding was considered abnormal and was attributed in part to the systemic axis deviation and in part to coronary artery disease, though there were no clinical findings to confirm this latter impression. No follow-up visit was obtained.

CASE 9.—J. R. (No. 22613), a 71-year-old rabbi, was followed in this hospital from the age of 62 to 74 years. His complaints were primarily related to a benign prostatic hypertrophy, for which he received two transurethral prostatic resections at the age of 62 years and again at the age of 68 years. The initial physical examination revealed dextrocardia with situs inversus, which was confirmed by x-ray examination of the chest and by a gastrointestinal x-ray series. The blood pressure was 120/78. No cardiac abnormalities other than the dextrocardia were noted. He had no complaints referable to his cardiorespiratory system. The electrocardiogram, first taken at the age of 65 years, showed a systemic axis deviation, but was otherwise entirely normal. Six years later, at the age of 71 years, he was seen in the medical clinic complaining of mild nonradiating precordial pressure, not related to exertion. The blood pressure was 140/88, and the heart and lungs were normal on physical examination. The electrocardiogram showed a slight increase in systemic axis deviation, T_2 had decreased slightly in amplitude, and RS-T_2 had become slightly depressed. These changes were attributed to the increase in systemic axis deviation. No further follow-up could be obtained.

CASE 10.—G. S. (No. 21933), a 22-year-old housewife, came to the clinic in 1933 complaining of constipation. Except for frequent colds during the winter, there were no complaints referable to the cardiorespiratory system. Physical examination revealed a dextrocardia with situs inversus confirmed by fluoroscopy of the chest and by a gastrointestinal x-ray series. The blood pressure was 100/70. The electrocardiogram showed a diphasic QRS_3, indicating a slight systemic axis deviation, but no other abnormalities were noted. No further follow-up was obtained.

CASE 11.—B. W. (No. 190951), a 36-year-old man, came to the hospital in 1938 complaining of recurrent lower abdominal pain. He had had an appendectomy complicated by peritonitis at the age of 14 years. On physical examination the blood pressure was 105/70, there was a congenital defect of the left eye and left optic nerve, dextrocardia was present, and there was a soft systolic murmur in the region of the cardiac apex. The liver was palpable at the left costal margin. An x-ray examination of the chest and gastrointestinal tract, including a barium enema, confirmed the presence of a situs inversus, but was otherwise normal. The electrocardiogram showed a systemic axis deviation but was otherwise entirely normal. A diagnosis of peritoneal adhesions was made, and the patient did not return for follow-up examination.

CASE 12.—B. L. (No. 16801), a 20-year-old girl, was admitted to the medical service in 1932 complaining of recurrent attacks of asthma, productive cough, congested nose, and a postnasal drip. Physical examination revealed congested nasal mucous membranes, dextrocardia with situs inversus, suggestive cyanosis of the lips, and a slight pitting edema of the ankles. The blood pressure was 90/64. An x-ray examination of the chest revealed dextrocardia and accentuated lung markings. X-ray examination of the sinuses showed a cloudy right antrum. A gastrointestinal x-ray series confirmed the presence of situs inversus. The electrocardiogram showed a systemic axis deviation, but was otherwise normal. Because of the ankle edema and slight cyanosis of the lips, the patient was digitalized, receiving 1.0 Gm. of digitalis in twenty-four hours. There was, however, no change in physical signs. Electrocardiograms taken after digitalization showed a slight decrease in amplitude of the T waves in Leads I and II, but there was no change in the level of the RS-T segments. She was discharged on her eighth hospital day, and did not return for follow-up examination.

CASE 13.—N. T. (No. 157391), a 31-year-old stone-cutter, was admitted to the medical service for treatment of bronchiectasis and chronic sinusitis. He gave a long history of nasal congestion, with polyps and postnasal drip, and of a chronic productive cough with frequent acute pulmonary infections. He has had several mild attacks of asthma. One sister had dextrocardia, sinusitis,

Fig. 7.—In this figure are reprinted the electrocardiograms from N. T. (Case 13), showing a tendency to pulmonic axis deviation. Fig. 7,*A* shows the three standard limb leads of the electrocardiogram as they were taken. Fig. 7,*B* shows the electrocardiogram with Lead I printed upside down and Leads II and III interchanged.

and bronchiectasis. On physical examination, the blood pressure was 110/75. There was congestion of the nasal mucosa, polyps were found in both nasal passages, and a nasal discharge was present. The chest was barrel shaped with limited but equal expansion on both sides, and numerous high- and low-pitched rhonchi were heard over both lungs. A dextrocardia was present without other cardiac abnormalities. There was marked clubbing of the fingers and toes. An x-ray examination of the chest showed dextrocardia and evidence of advanced bronchiectasis. X-ray films of the sinuses showed pansinusitis. The electrocardiogram (Fig. 7) showed a low amplitude of QRS_1, indicating a beginning pulmonic axis deviation, attributed to the chronic pulmonary disease, but there were no other abnormalities. He was treated for six weeks with postural drainage and discharged slightly improved. He did not return for follow-up examination.

RESULTS

By inverting Lead I and interchanging Leads II and III, we found that seven of the thirteen cases (Cases 1-3, 8, 9, 11, 12) had a systemic axis deviation. Three of these seven (Cases 1-3) had established hypertension or borderline hypertension, and the other four (Cases 8, 9, 11, 12) had no obvious explanation for their axis deviation. This is, however, a not uncommon finding in subjects with normally placed hearts. Three of the thirteen cases (Cases 4, 6, 10) had a low amplitude of QRS_3 or a diphasic QRS_3, indicating a beginning systemic axis deviation. One of these three (Case 4) was six months pregnant, and the tendency to systemic axis deviation disappeared subsequent to delivery; one (Case 6) had a long-standing anemia with x-ray evidence of enlargement of the systemic ventricle; and one (Case 10) had no obvious explanation for this finding. Two of the thirteen cases (Cases 5 and 7) showed no axis deviation. One of the thirteen cases (Case 13) showed a low amplitude of QRS_1, indicating a beginning pulmonic axis deviation, and this was attributed to chronic pulmonary disease which led to pulmonic ventricular strain.

Three of the thirteen cases (Cases 1, 2, 8) showed abnormalities of the T waves in the three limb leads. In one (Case 1) T_1 and T_2 were negative and coved, in one (Case 2) T_1 was negative and coved, and in one (Case 8) T_1 was of low amplitude.

The multiple precordial leads showed abnormalities in three cases (Cases 1-3). It is recalled that the interpretation of the chest derivations did not differ from that employed in subjects with a normally placed heart. These three cases showed negativity and coving of the T waves in one or more of the leads taken from the right side of the chest. One of these (Case 1, Fig. 3), whose chest x-ray is reproduced in Fig. 1, had hypertension and coronary artery disease, one (Case 3) had a mild hypertension, and one (Case 2), whose electrocardiograms are reproduced in Figs. 4, 5, and 6, had no obvious explanation for the abnormality.

In normal subjects, it has been observed that precordial leads taken from the right side of the chest may show negative and coved T waves.[8] It was expected, therefore, that in cases of dextrocardia the precordial leads taken from the left side of the chest might show negative and coved T waves. Six of the seven cases showed this finding, an example of which is shown in Fig. 2, and it was considered normal. One patient (Case 1), however, had upright T waves in the

leads taken from the left side of the chest (Fig. 3), and this was associated with negativity and coving of the T waves in Leads $CF_2(R)$, $CF_3(R)$, and $CF_4(R)$ taken from the right side of the chest. This was considered abnormal, and thought to be associated with the hypertension and coronary artery disease which this patient had.

DISCUSSION

Dextrocardia with situs inversus is not a common condition. The incidence varies in different reports from 1 in 11,000 to 1 in 35,000. In the New York Hospital, since 1932, approximately 460,000 patients have been seen, among which there have been thirteen cases of dextrocardia with situs inversus, making an incidence of 1 in 35,000. Of course, x-ray examinations were not made of all patients and the abnormality may have escaped diagnosis in some cases.

It is not our purpose to discuss the general aspects of transposition of the viscera; it has been reported, however, that congenital defects are more common in this group. One of our thirteen patients had a congenital anomaly of the left eye. It has also been stated that bronchiectasis and pansinusitis are more common in this group than in the population at large, the combination of dextrocardia, sinusitis, and bronchiectasis being known as Kartagener's triad. Of the thirteen patients, four had sinusitis, confirmed by x-ray examination of the sinuses (Cases 1, 5, 12, 13). One of these four (Case 13) had a proved bronchiectasis; one (Case 12) had a chronic productive cough with increased lung markings in the x-ray film of the chest, which was suggestive of early bronchiectasis; and one (Case 5) had a history of chronic cough for many years, though x-ray changes characteristic of bronchiectasis were not demonstrated in the x-ray films of the chest and the cough had disappeared by the time our follow-up examination was made.

The individual with situs inversus is subject to the same diseases as individuals with normally placed hearts, and it is apparent that a certain number of them will suffer from organic heart disease. If these subjects acquire heart disease, the electrocardiogram becomes a useful diagnostic aid, after the presence of dextrocardia has been established. For instance, by transposing the leads as we have suggested before interpreting the electrocardiogram, it can be used to follow the progress of the patient with myocardial infarction, with coronary artery disease, or with hypertension, without the necessity of making a mental allowance for the dextrocardia.

The use of this means of analyzing the electrocardiogram in dextrocardia makes interesting a review of some of the cases reported in the literature. The case reported by Smith and Horton[5] showed a systemic axis deviation with deviations of the RS-T segments which were probably significant as indicating a definite electrocardiographic abnormality, of which the authors made no mention.

In the case reported by Manchester and White,[7] a case of hypertension and coronary artery disease, it was stated that the amplitude of QRS_1 in a negative direction in the untransposed leads was great enough to indicate ventricular hypertrophy in addition to the dextrocardia. When this record is interpreted in the light of the procedure we have used, systemic axis deviation is not present.

Lys's[8] case of dextrocardia with complete heart block and a patent interventricular septum showed enlargement of the pulmonary side of the heart in the x-ray film of the chest. The electrocardiogram, when transposed, showed, according to our analysis, a marked pulmonic axis deviation. This characteristic did not have attention directed to it when the conventional method of reading the electrocardiogram in dextrocardia was used.

A review of our thirteen cases also shows that this technique contributed a great deal of information. In most of the cases the additional information is exactly what one might expect from a similar electrocardiographic study of a comparable series of patients with normally placed hearts. Thus, the patient in Case 1 had hypertension, x-ray evidence of an enlarged systemic ventricle, and electrocardiographic evidence of systemic ventricular hypertrophy and coronary artery disease.

Case 2 is interesting in that at the age of 24 years, with no symptoms or signs of heart disease, the patient showed, on reversing the leads, a negative and coved T_1 (Fig. 4), an abnormality for which we have no explanation. At the age of 38 years, when the electrocardiogram was repeated (Fig. 5), T_1 was still partly negative and coved, and the T waves in Leads $CF_2(R)$, $CF_3(R)$, $CF_4(R)$, $CF_5(R)$, and $CF_6(R)$ (from the right side of the chest) were all negative, or partly negative, and coved. There were still no symptoms or signs referable to the heart, and an x-ray examination of the chest showed no cardiac enlargement. The only physical finding of interest was that, at the time of his first return visit, his initial blood pressure reading was 176/96; this fell rapidly to 134/82, and at the time of a revisit four months later the blood pressure was again within normal limits. The repeat electrocardiogram (Fig. 6), however, with the exception of the systemic axis deviation, was entirely normal, with upright T waves in all leads except those taken from the left side of the chest.

The exercise tolerance test and anoxemia tests induced insignificant changes in the electrocardiogram. The only change in symptomatology between the last electrocardiogram and the first two was that on the first two occasions he was having many complaints referable to his gastrointestinal tract, and on the last occasion he had been free of symptoms for several months. Reflex changes in coronary circulation from gastrointestinal disturbances have been described, and this might have been the basis for his electrocardiographic abnormalities. This must, however, remain for the present time within the realms of speculation.

The patient in Case 3 exhibited mild hypertension, and the x-ray film of the chest showed slight systemic ventricular hypertrophy. The electrocardiogram indicated slight systemic axis deviation.

The patient in Case 4 gave a history suggestive of coronary insufficiency developing four and one-half months after termination of a full-term pregnancy which had been complicated by a mild toxemia of pregnancy associated with a transient hypertension. We were able to demonstrate, however, by means of a negative exercise tolerance test and a negative anoxemia test, that her complaints were probably not related to her cardiovascular system.

The patient in Case 6 showed slight systemic ventricular enlargement by x-ray examination of the chest, possibly associated with the long-standing anemia, and the electrocardiogram showed only a slight systemic axis deviation without other abnormalities.

The patient in Case 8 gave no history suggestive of cardiorespiratory disease, but the electrocardiogram showed systemic axis deviation and a low amplitude of T_1. This latter finding was attributed to the systemic axis deviation, and was also suggestive of coronary artery disease, an interpretation that was not made at the time of the original reading according to conventional methods.

The patient in Case 13 showed a slight pulmonic axis deviation (Fig. 7) which, in a man of 31 years, is probably abnormal. This observation, combined with clinical and x-ray evidence of chronic pulmonary disease (bronchiectasis), indicates that he had pulmonic ventricular strain secondary to the pulmonary disease. This was particularly important in this case because the x-ray examination of the chest showed no cardiac enlargement. The electrocardiogram thus gave the only evidence of heart strain and attention would not have been directed to it by the conventional method of interpretation.

SUMMARY AND CONCLUSIONS

It is our opinion that the electrocardiogram has not been used to greatest advantage in cases of dextrocardia with situs inversus. In reports of dextrocardia with situs inversus complicated by hypertension, myocardial infarction, coronary artery disease, and rheumatic heart disease, there has been confusion in interpretation and in terminology.

A new method of approach to the interpretation of the electrocardiogram in dextrocardia has been presented, and a more suitable terminology has been devised. It is our practice to invert Lead I and to interchange Leads II and III before attempting interpretation. We have also substituted the terms pulmonic and systemic in describing axis deviation or ventricular hypertrophy, thus avoiding the terms right (pulmonic) and left (systemic) which are interchanged in dextrocardia. In this way a routine electrocardiographic interpretation can be made just as for the person with the normally placed heart.

Thirteen cases of dextrocardia with situs inversus have been presented with descriptions of the electrocardiographic findings. Seven of these were studied by means of ten precordial leads derived from both sides of the chest. Systemic axis deviation was present in seven, slight or beginning systemic axis deviation in three, slight pulmonic axis deviation in one, and no axis deviation in two. Abnormalities of the T waves in the limb leads and multiple precordial leads were noted in four patients; two of these had hypertension, one had possible coronary artery disease, and in one there was no adequate explanation for the abnormalities.

The impression that negativity and coving of T waves, derived from the left side of the chest in cases of dextrocardia with situs inversus, are normal findings is supported by the fact that six of our seven cases showed this finding.

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A STUDY OF ALLEGED INTERCORONARY REFLEXES FOLLOWING CORONARY OCCLUSION

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THE explanation of sudden cardiac death has baffled investigators for many years, principally because of the lack of correlation between the severity of the necropsy findings and the swiftness of the patient's demise. A hypothesis of reflex coronary vasoconstriction has been advanced to account for such deaths, and this explanation has been accepted by many clinicians. The hypothesis has been succinctly stated by LeRoy and Snider[1] in these words: "The sudden death of a patient with infarction of the myocardium is due to reflex coronary vasoconstriction whose stimulus is the infarct, whose afferent pathway is the cardiosensory innervation and whose efferent pathway is the vagus. The result of this reflex vasoconstriction in a susceptible person is fatal ventricular fibrillation."

The evolution of such a view apparently had its beginning in the investigations of Manning and co-workers,[2] whose experiments showed that ligation of a coronary artery was much more serious, as judged by mortality rates, in unanesthetized than in anesthetized dogs. It was suggested that nervous impulses (via pain fibers) from the primary ischemic area caused a temporary reflex vasospasm of other coronary arteries resulting in secondary ischemic areas. The difference in results between anesthetized and unanesthetized animals was explained by assuming that anesthesia abolished the reflex. In a subsequent paper, the same investigators tested their hypothesis by interrupting the logical afferent nervous pathways.[3] Bilateral removal of the stellate and first through fifth thoracic ganglia materially improved the chances of survival for the first twenty-four hours following the ligation of a coronary artery. In their opinion, the hypothesis was strengthened but not proved.

Later, LeRoy and co-workers,[4] using essentially the same technique as Hall and co-workers, except that the experiments were done under morphine-nembutal anesthesia, further tested the hypothesis by observing the effects of xanthine derivatives and atropine on the mortality rate. They found that theobromine sodium acetate, aminophylline, and atropine, or a mixture of the last two drugs, reduced the mortality rate after coronary occlusion from 70 per cent to 23 to 56 per cent. This beneficial effect was ascribed to the reduction of secondarily ischemic areas through the direct or indirect vasodilator action of the drugs.

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Although it seems to be demonstrated that the mortality rate following coronary occlusion can be materially decreased by sympathectomy in some form,[3,5-8] or by the use of coronary vasodilator drugs,[4,9] it appeared to us that it was by no means proved that the higher mortality rate of unanesthetized dogs following coronary occlusion was due to a reflex vasospasm of other coronary arteries, the positive statements of LeRoy and associates notwithstanding. Proof of the validity of the hypothesis of reflex coronary vasoconstriction demands unequivocal evidence that coronary flow is reduced in an artery adjacent to the occluded artery, that such reduction is in fact due to vasoconstriction, and that the reduction in blood flow is sufficient to impair fatally the function of the heart. Before such a hypothesis is accepted as fact by repetition in uncritical reviews, textbooks, and pharmaceutical advertising, it seems urgent to examine the experimental evidence from several points of view.

A search of the literature at the beginning of this investigation failed to disclose any experiments in which the coronary flow in one artery was measured while an adjacent artery was occluded, although there are allusions to such experiments.[1,4] Accordingly, we performed the experiments reported in this paper in an effort to prove or disprove the hypothesis. In addition to drawing conclusions from our own experiments, we have sought pertinent facts in studies on coronary reflexes, on myocardial electrical activity, and on the mechanism of ventricular fibrillation. Finally, we have interpreted the results of the experiments of Manning, McEachern, and Hall and those of LeRoy, Fenn, and Gilbert in the light of the evidence as we see it.

METHODS

Coronary flow was estimated by use of the optically recording flowmeter illustrated in Fig. 1 and more fully described elsewhere.[10] The cannula, *A*, was inserted into a coronary artery and the artery perfused with normally oxygenated blood from the left subclavian artery through the short external circuit, *B*. Before making a flow record, the pressure in the reservoir, *C*, was increased to about 10 mm. Hg above existing mean aortic pressure and stopcocks, *I* and *F*, closed. Opening stopcock *J* and simultaneously clamping tube *B* allowed blood to flow into the artery from the reservoir; the rate of pressure fall in the reservoir, recorded by the optical manometer *G*, was proportional to the rate of inflow. Flows were calculated from the record at existing mean aortic pressures.

Dogs were anesthetized with 3.0 mg. morphine per kilogram of body weight subcutaneously and either 200 mg. sodium barbital or 70 mg. chloralose per kilogram intravenously.

The chests were opened under moderate artificial respiration and the hearts suspended in a pericardial cradle, the usual precautions associated with open chest experiments being observed. Either the left anterior descendens or the right coronary artery was prepared for ligation, with care taken not to disturb the coronary sheath any more than necessary to pass the ligature. In some experiments the coronary artery was prepared for ligation in two places, the more distal ligature being tied first and the more proximal one being tied when it

became apparent that the first occlusion had no effect on flow in the adjacent artery.

The dogs were heparinized and a cannula inserted into either the right coronary artery near its origin or the left anterior descendens about 2.0 cm. from its origin, the perfusing blood being supplied from a cannula previously placed in the left subclavian artery.

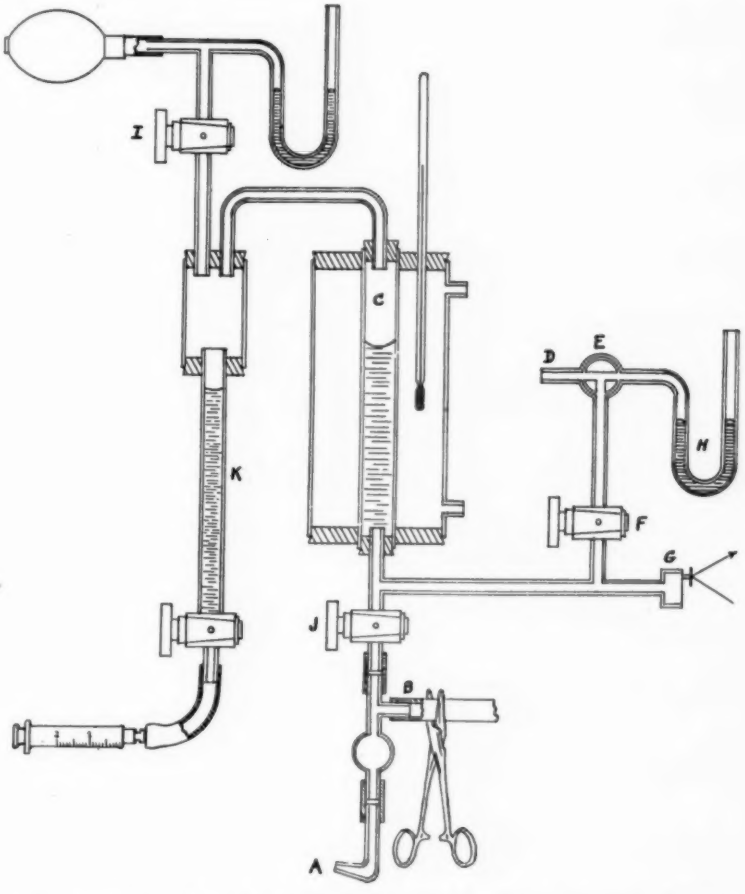

Fig. 1.—Apparatus used for estimating coronary inflow. Described in text.

Aortic pressures were recorded by an optical manometer of adequate frequency and sensitivity via a cannula passed down a carotid artery to the arch of the aorta. Mean aortic pressures were determined from the optical records by integration of the pressure pulses.

Three to six control flows were obtained over a period of twenty to sixty minutes before ligating, following which flows were measured one, five, and every ten minutes thereafter for a period up to two hours.

RESULTS

Our first experiments were conducted with morphine-sodium barbital anesthesia. Seven such experiments were performed, two of which were discarded because the control mean aortic pressures were less than 100 mm. Hg, which we consider poor preparations. Right coronary flows were measured in three experiments and flow in the anterior descendens artery in two experiments. The data obtained from four of these experiments are plotted in Fig. 2, the fifth experiment being omitted to conserve space.

The plot of Experiment 1 shows the changes in right coronary flow, heart rate, and aortic pressure after occlusion of the anterior descendens system. Flow in the right coronary artery decreased to 94 per cent of average control flow (*A*) within one minute after occlusion of a large branch of the anterior descendens artery, the mean aortic pressure decreasing only slightly and the heart rate remaining constant. During the next seventeen minutes (*A-B*) aortic pressure increased from 124 to 133 mm. Hg, heart rate decreased slightly, but coronary flow meanwhile decreased to 82 per cent of average control flow. From Point *B* to Point *C* mean aortic pressure declined slightly, heart rate remained constant, and there was no further significant decrease in coronary flow. In an attempt to intensify the decrease in flow in the right coronary artery, the main trunk of the left ramus descendens was occluded (see diagram on plot). However, this maneuver resulted in an immediate increase in right coronary flow despite a lowered mean aortic pressure and only a slight decrease in heart rate (*C-D*). Over the next thirty minutes (*D-E*) the right coronary flow slowly decreased to 75 per cent of the average control flow. Mean aortic pressure declined moderately (123 to 116 mm. Hg), but later increased to control level during the latter part of the period *D'-E*.

Changes in mean coronary flow are usually interpreted in terms of the effects of three variables: (1) mean aortic pressure, (2) heart rate, and (3) peripheral resistance, which is determined by extravascular and vasomotor changes. It is agreed that coronary flow bears a direct relationship to mean aortic pressure, but the effect of changes in heart rate on flow is not so well established.[11] From a dynamic point of view it would appear that slowing of the heart favors an increase in flow by virtue of the aortic diastolic pressure acting over a longer period, during which time extravascular compression is at a minimum. Vasomotor activity can be assessed only when mean aortic pressure and heart rate are constant or when the directional change in flow is opposite to that normally produced by the change in the other two variables.

Analyzing the results of Experiment 1 (and subsequent experiments) on this basis, it can be seen that during the periods *A-B* and D'-*E* there is some indication of coronary vasoconstriction, since coronary flow decreased while mean aortic pressure increased and heart rate decreased. Under such conditions one would expect an increase in coronary flow unless this tendency was opposed by coronary vasoconstriction. On the basis of this single experiment one could conclude that it offers support for the hypothesis of reflex coronary vasoconstric-

tion. However, analysis of further experiments reveals that it would be erroneous to draw a general conclusion from Experiment 1.

The plot of Experiment 2 (Fig. 2) shows another pattern of flow in the right coronary artery under conditions very similar to those present in Experiment 1. Right coronary flow increased immediately after occlusion of a large branch of the left descendens at *A*. This increase in flow was probably due to the increase in mean aortic pressure (98 to 110 mm. Hg), since the heart rate increased

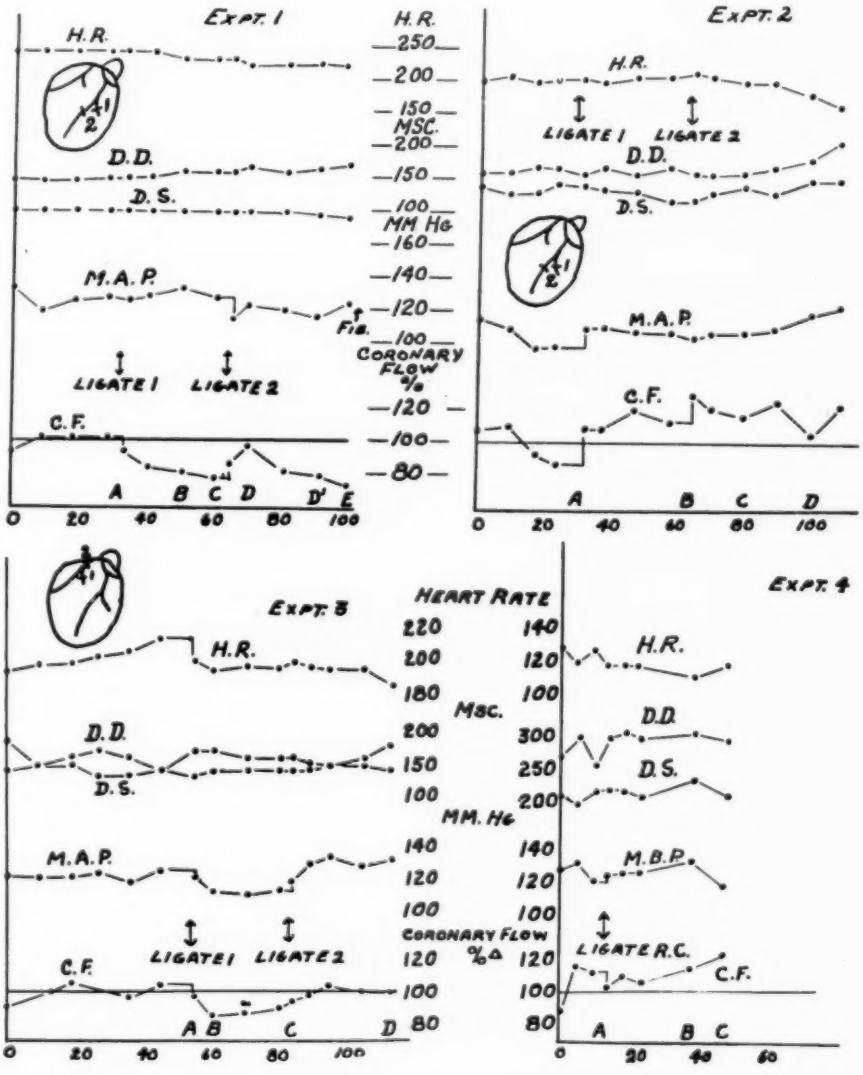

Fig. 2.—Effect of coronary occlusion on flow in an adjacent artery. Morphine-sodium barbital anesthesia. Ordinates, time in minutes; abscissae as indicated. *H.R.*, heart rate; *D.D.*, duration of diastole; *D.S.*, duration of systole; *M.A.P.*, mean aortic pressure; *C.F.*, coronary flow; *R.C.*, right coronary; *L.D.*, left descendens.

slightly. Throughout the period *A-C*, right coronary flow was substantially in excess of the average control flow. The elevated mean aortic pressure was constant or declining slightly and heart rate was also essentially constant. Occlusion of the main trunk of the anterior descendens system at *B*, so as to deprive a larger part of the myocardium of its blood supply and to intensify any reflex effects, failed to decrease the right coronary flow to control flow level at any time. The cause of the temporary reduction in flow at Point *D*, at which time mean aortic pressure was increasing and heart rate decreasing, is unexplained. However, it did not persist or appear to affect the function of the heart in any way.

In Experiment 2, occlusion of one coronary artery materially increased the flow in an adjacent artery. This result probably occurred because of the slight but persistent increase in the mean aortic pressure after occlusion. There is no clear-cut evidence of coronary vasodilatation, although it might have occurred. There is also the possibility that the lowered coronary pressure in the left descendens system distal to the point of occlusion set up a favorable pressure gradient so that blood passed from the right coronary system to the left via collateral channels.

Coronary flow was measured in the left anterior descendens in Experiments 3 and 4 before and after occlusion of the right coronary artery. Flow decreased immediately after occlusion of a large branch of the right coronary artery in Experiment 3, but the decrease in flow was concomitant with a decrease in mean aortic pressure (125 to 120 mm. Hg) and a slight decrease in heart rate. The heart rate, as a matter of fact, was remarkably constant throughout the experiment although there were marked changes in the relation of the length of systole to diastole. Coronary flow continued to decrease following the first occlusion (*A-B*), but the decrease in flow was accompanied by a further decrease in mean aortic pressure. As a matter of fact, the changes in coronary flow throughout the experiment faithfully reflect changes in mean aortic pressure, the correspondence not being modified by occlusion of the main trunk of the right coronary artery at *C*. At Point *D*, the flow in the left descendens was equal to the average control flow, although mean aortic pressure was somewhat greater. The moderate reduction in flow during the period *A-C* in this experiment was probably due to the reduction in mean aortic pressure rather than to coronary vasoconstriction.

The right coronary artery was ligated close to its origin in Experiment 4 and flow measured in the left anterior descendens. There was little change in the rate of flow immediately after occlusion, although heart rate decreased from 130 to 120 beats per minute and mean aortic pressure increased from 120 to 124 mm. of mercury. Mean aortic pressure increased slowly over the next twenty-seven minutes (124 to 133 mm. Hg), heart rate declined slightly (120 to 113 beats per minute). The coronary flow during this interval (*A-B*) increased to 10 per cent above average control level and continued to increase after mean aortic pressure had decreased (*B-C*). The directional changes in mean aortic pressure and coronary flow in this experiment are such that no clear-cut evidence of coronary vasoconstriction can be deduced.

Summarizing the results obtained in this group of experiments, one experiment showed evidence of a coronary vasoconstriction, one experiment showed a reduction in coronary flow due probably to a decrease in mean aortic pressure, one experiment showed little change in flow after occlusion (Experiment 5, not illustrated) and two experiments showed an increase in coronary flow after ligation of an adjacent coronary artery. These experiments, therefore, do not offer conclusive evidence in favor of the reflex coronary vasoconstriction hypothesis. On the contrary, there is evidence that in a high percentage of cases an increase in coronary flow can be expected when an adjacent artery is occluded.

Since it has been suggested that morphine-ether anesthesia abolishes reflex coronary vasoconstriction,[2] there remained the possibility that morphine-barbital anesthesia might act in a similar manner. Therefore, in a second group of five dogs we used morphine-chloralose anesthesia because chloralose is reputed to exaggerate reflexes.[12] The eye, auditory, tendon, and cardiovascular reflexes were very active with the dosage we used and we see no reason to assume that coronary reflexes were in any way impaired as a result of anesthesia. As a matter of fact, LeRoy and co-workers[4] used morphine-nembutal anesthesia in their studies on coronary occlusion, administering the nembutal "until the corneal reflex just disappeared." They found no difference in mortality between these and unanesthetized dogs. We have always considered the disappearance of the corneal reflex as a sign of a rather deep plane of anesthesia and have seldom observed this even with our morphine-sodium barbital anesthesia.

Fig. 3 shows plots of four experiments from the morphine-chloralose group of dogs. In general, this group was characterized by very irregular heart rates, the relation between the length of systole and diastole being extremely variable. The heart rate of dogs anesthetized with morphine-barbital did not exhibit such wide fluctuations, a fact of considerable importance when attempting to explain changes in coronary flow.

The plot of Experiment 6 in this group shows a decreasing coronary flow, mean aortic pressure, and heart rate during the control period, *A-B*. Immediately after occlusion of the left descendens (*B-C*) the flow in the right coronary increased from 78 to 86 per cent of average control flow, the mean aortic pressure and heart rate increasing only slightly. During the next ten minutes (*C-D*) right coronary flow decreased to 75 per cent of average control flow despite a slight increase in mean aortic pressure and a decrease in heart rate from 136 to 125 beats per minute. It is worthwhile to point out that the rate of coronary flow at Point *D* was the lowest measured during the experiment, yet it was not significantly lower than the control flow immediately preceding the occlusion of the left anterior descendens artery. Coincident with an increase in heart rate from 125 to 164 beats per minute, the coronary flow increased from 75 to 112 per cent of control flow (*D-E*). Mean aortic pressure increased only slightly during the same period. Following the marked increase in coronary flow, a decrease to 82 per cent of control flow occurred (*E-F*), mean aortic pressure gradually increasing while heart rate again slowed.

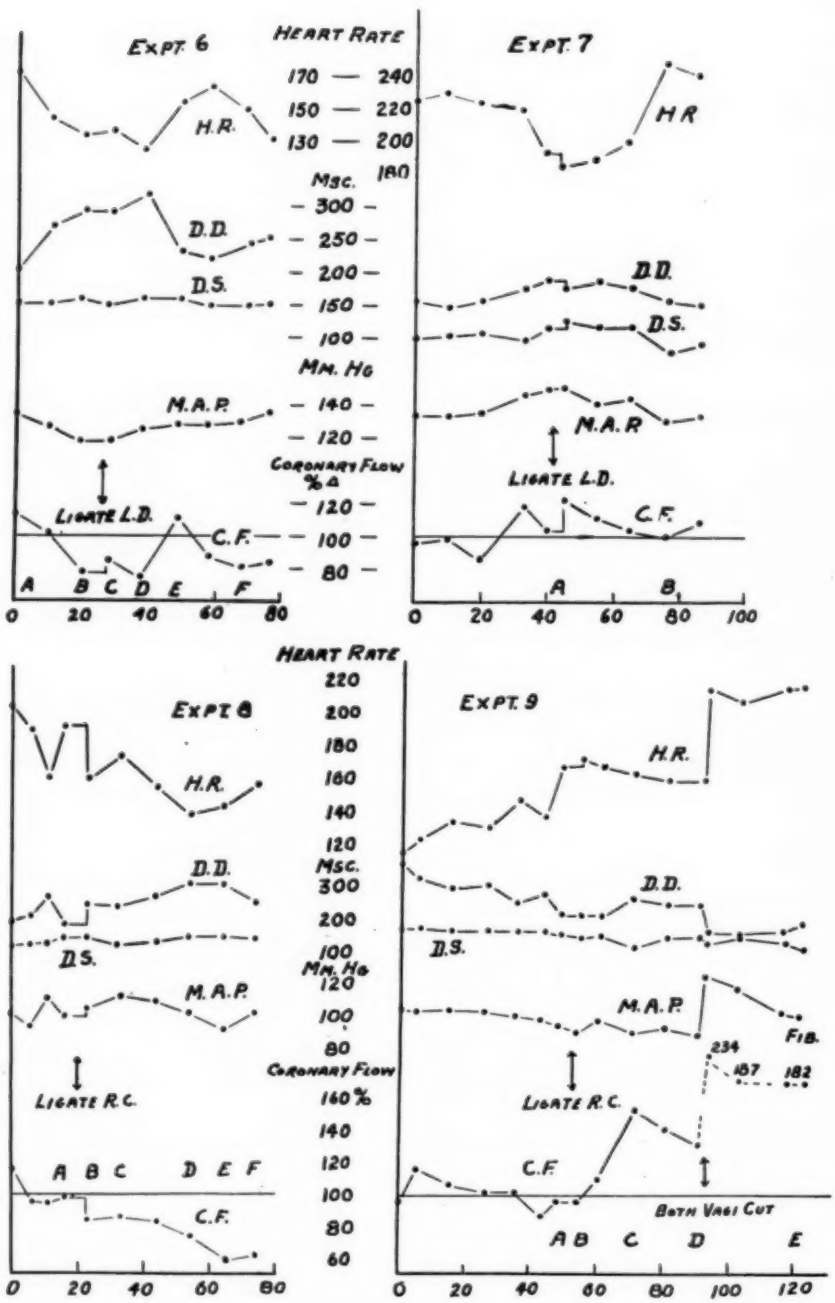

Fig. 3.—Effect of coronary occlusion on flow in an adjacent artery. Morphine-chloralose anesthesia. Ordinates, time in minutes; abscissae as indicated. *H.R.*, heart rate; *D.D.*, duration of diastole; *D.S.*, duration of systole; *M.A.P.*, mean aortic pressure; *C.F.*, coronary flow; *R.C.*, right coronary; *L.D.*, left descendens.

The progressive decrease in coronary flow during the control period, *A-B*, makes the interpretation of subsequent changes in flow very difficult. The fall in mean aortic pressure from 134 to 117 mm. Hg during this time may account for the decrease in flow, but if so, then the marked deceleration of the heart, 170 to 133 beats per minute, had little or no effect on flow. A paradoxical situation also prevails during the period *D-E*. Here the mean aortic pressure increase was insignificant; the heart rate accelerated from 125 to 154 beats per minute, yet coronary flow increased from 75 to 112 per cent of average control flow. These circumstances, according to our methods of analysis, call for a decrease in flow, unless coronary vasodilatation occurred. If these marked variations in flow do represent vasomotor activity, then it is clear that any vasoconstriction that might have occurred subsequent to occlusion was not sufficient to reduce coronary flow to less than the lowest flow recorded before occlusion. Therefore, we do not feel that this experiment supports the hypothesis of reflex coronary vasoconstriction.

The plot of Experiment 7 (Fig. 3) shows again the effect of occlusion of the left anterior descendens on flow in the right coronary artery. Great variation in heart rate characterizes this experiment. Following occlusion of the left anterior descendens at *A*, the changes in mean aortic pressure and heart rate were insignificant. The right coronary flow increased immediately after occlusion indicating possible vasodilatation, but in view of the fluctuations in control flow it is not certain that the increase was a result of the occlusion. Following the initial increase to 123 per cent of average control flow, the trend was slowly downward (*A-B*), but never to less than average control flow. The decrease in right coronary flow was undoubtedly due to the decrease in mean aortic pressure and probably also to the marked increase in heart rate. Since the changes in flow after occlusion indicated either a vasodilatation, or are explained by changes in mean aortic pressure, this experiment offers no evidence of coronary vasoconstriction following occlusion. Furthermore, flow was not observed to decrease to less than the average control flow at any time.

Experiment 8 (Fig. 3) supports the hypothesis of reflex coronary vasoconstriction more strongly than any other experiment in this group. Immediately after ligation of the right coronary artery, the flow in the left descendens decreased from 98 to 84 per cent of the average control flow (*A-B*). Mean aortic pressure increased slightly (100 to 104 mm. Hg) and the heart rate slowed markedly (190 to 156 beats per minute), most of the deceleration being due to an increase in the length of diastole. If one assumes that an increase in the length of diastole increases coronary flow, then the decrease in coronary flow during this period must have been due to vasoconstriction, since mean aortic pressure increased slightly. Following the initial decrease in coronary flow, the flow remained constant (*B-C*) for a short period, although mean aortic pressure increased from 104 to 112 mm. of mercury. During the same period heart rate increased from 156 to 172 beats per minute. Starting at Point *C* and continuing to Point *D*, mean aortic pressure, heart rate, and coronary flow all declined slowly. At Point *D* the heart rate accelerated slightly but the decrease in mean aortic pressure

and coronary flow continued. As would be expected, coronary flow decreased more rapidly, indicating that the deceleration of the heart during the period *C-D* had prevented a more rapid decrease in flow. Evidence of coronary vasoconstriction during this period cannot be deduced unequivocally. Finally, the decrease in coronary flow which had reached a level of 58 per cent of average control flow was halted by an increase in mean aortic pressure (*E-F*). This is some indication that the decrease in flow between the Points *C* and *E* was due to a loss of aortic pressure head, but this observation does not rule out the possibility of vasoconstriction as a contributing factor.

Applying the classical concepts of interpreting changes in coronary flow as outlined in the beginning, it can be concluded that only the initial decrease in flow (*A-B*) can possibly be attributed to coronary vasoconstriction. All subsequent changes can be explained qualitatively by the interaction of changes in heart rate and mean aortic pressure. Quantitatively it is not so simple, for the fact remains that flow was finally reduced to 62 per cent of average control flow with mean aortic pressure and heart rate not greatly different from that of the control period. It would appear that this experiment shows that coronary flow can be reduced in one artery by occlusion of an adjacent artery, but offers no clear-cut evidence that vasoconstriction is the mechanism entirely responsible for the reduction.

The fourth experiment in this group, Experiment 9 (Fig. 3) showed an unmistakable increase in flow in the left anterior descendens following occlusion of the right coronary artery. Immediately after occlusion (*A-B*) there was no change in flow, aortic pressure decreasing slightly and heart rate accelerating a few beats per minute. However, during the next seventeen minutes (*B-C*) the coronary flow increased from 96 to 153 per cent of the control flow, although the changes in mean aortic pressure and heart rate were negligible. This certainly indicates either vasodilatation or the opening up of collateral circuits. From *C* to *D* the coronary flow gradually decreased in spite of the fact that aortic pressure was maintained at a constant level and heart rate slowed, but the flow was still 30 per cent above the average control flow.

Both vagus nerves were cut in Experiment 9, as indicated at Point *D*. Immediate increases in mean aortic pressure, coronary flow, and heart rate occurred. The increase in flow persisted after the mean aortic pressure had returned to control level, finally leveling off at about 82 per cent above control flow. The experiment was terminated by a spontaneous ventricular fibrillation at Point *E*. Here is one case in which fibrillation occurred in the presence of an increased coronary flow.

In summary, of the five experiments in the morphine-chloralose group, only Experiment 8 gave evidence of coronary vasoconstriction after occlusion. Flow was reduced below average control flow in Experiment 6, but there was no evidence that the reduction in flow resulted from an augmentation of vasoconstriction after occlusion. Flow increased in Experiments 7 and 9. No change in flow that could be attributed to vasoconstriction was found in the fifth experiment (Experiment 10, not illustrated). The results of this group of experiments

do not differ from those obtained in the morphine-barbital group. In both groups, only one dog of five exhibited evidence of coronary vasoconstriction after occlusion, and two of five responded with an increase in coronary flow.

Results similar to our own were obtained recently by Eckenhoff and associates,[13] using the same type of preparation but recording coronary flow with a bubble flowmeter.

DISCUSSION

After long consideration, we have concluded that our experimental data do not provide acceptable proof of the hypothesis of reflex coronary vasoconstriction as a factor in sudden cardiac death. This conclusion was reached in spite of the fact that there was evidence of vasoconstriction in two of the ten experiments. These positive results are discounted for the following reasons: (1) The heart which showed the greatest reduction in coronary flow after occlusion did not fibrillate (Experiment 8), whereas in other experiments hearts which did not show a reduction in coronary flow did fibrillate (Experiments 1, 5, 9, and 10). (2) We question whether the extent of reduction in flow in Experiments 1 and 8 was sufficient to produce ischemia in that area of the myocardium not directly affected by the occlusion.

The doubt expressed by the latter point has its basis in several different lines of evidence. First, it has been shown recently that coronary flow can be reduced to as much as 70 per cent below control flow for relatively long periods without producing ventricular fibrillation.[10] A survey of the literature indicates that a maximum reduction in flow of about 35 per cent can be expected when coronary flow is reduced by the stimulation of nerves, regardless of the nerve stimulated, method of measuring flow, or the criterion of vasomotor activity employed.[14-17] To the best of our knowledge, ventricular fibrillation as a result of stimulation of any afferent nerve has not yet been demonstrated experimentally.

Second, myocardial ischemia is known to be a powerful vasodilator which produces great and prompt increase in coronary flow.[18] If the hypothesis of reflex coronary vasospasm following coronary occlusion is true, then the vasoconstriction must produce and maintain myocardial ischemia which in itself is the most effective coronary vasodilator known. This interesting situation has never been demonstrated experimentaliy.

If ischemia can be produced and maintained by coronary vasoconstriction, it is reasonable to expect that local lead electrograms from the ventricular surfaces should furnish important information, since sudden coronary occlusion produces prompt and predictable changes in the electrocardiogram.[19-21] If areas outside of the primary ischemic area are rendered ischemic by reflex coronary vasoconstriction, then local leads from such areas should show progressive alteration in the action potentials similar to the early changes recorded directly from the primary potentially infarcted area.

Fortunately, such electrograms are available from experiments which heretofore have not been analyzed with regard to the problem of reflex coronary vasospasm. Harris and Guevara Rojas[22] studied action potentials throughout the

ventricles during occlusion of the left anterior descendens artery, searching for the probable locus of impulses initiating ventricular fibrillation. The locus of the ectopic impulses was found to be the border zone between the ischemic and nonischemic areas. Their investigations clearly show that the action potentials in areas outside the boundary zone of the primary ischemic area remain absolutely normal in form and temporal relations except when the impulse arises from an ectopic locus and is conducted by aberrant pathways.

Dr. Harris has kindly permitted us to illustrate this point with one of their unpublished records. Fig. 4 shows local leads from three areas of the ventricle after an occlusion which eventuated in ventricular fibrillation. It will be observed that the voltage and form of the action potential in the myocardium just outside the boundary of the ischemic area (Lead I) is normal *right up to the last normally initiated impulse preceding ventricular fibrillation* (marked *X*). This certainly indicates that electrical signs of ischemia are confined strictly to the area supplied by the ligated coronary vessel and are not reflected by the myocardium as a whole.

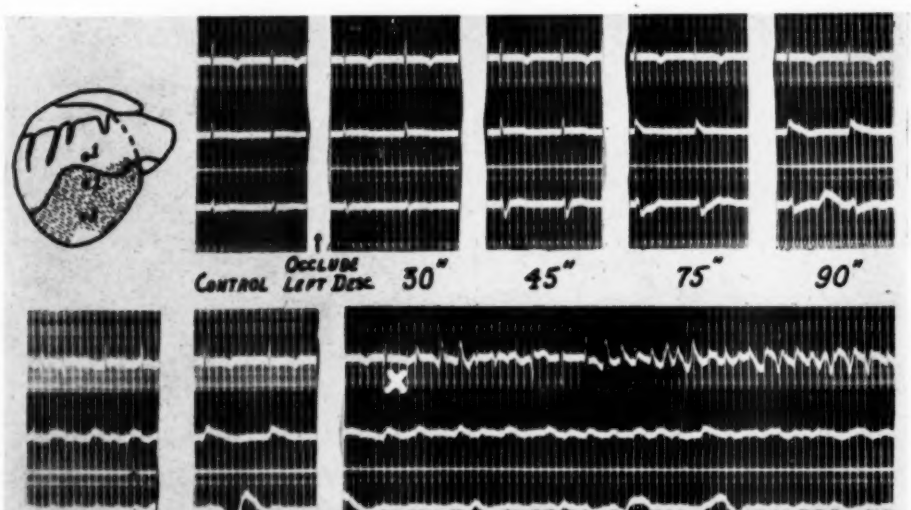

Fig. 4.—Serial records of action currents recorded from the ventricular surfaces before and after occlusion of the left descendens artery. Leads I, II, and III from top to bottom. The positions of the bipolar contiguous electrodes are indicated on the diagram at the left. The shaded part of the diagram indicates the ventricular area that appeared intensely cyanotic. Discussion in text.

Since it has been stated that sudden cardiac deaths are caused by ventricular fibrillation, the mechanism of initiation of fibrillation and its prevention by the use of drugs is of great interest. Studies on the mechanism of experimentally induced fibrillations indicate that the fibrillation is always preceded by an accelerating series of ectopic discharges.[23] Such a series of discharges slows con-

duction time and shortens the refractory period throughout the entire responding myocardium and furnishes the basis for the establishment of continuous conduction circuits. The sequence of events leading to ventricular fibrillation after sudden coronary occlusion would seem to occur in the following order: The boundary of the ischemic area becomes highly excitable and discharges ectopic stimuli. A series of accelerating ectopic stimuli acts to decrease the refractory period and slow conduction throughout the responding myocardium, conditions which are prerequisite to re-entry of impulses, and ventricular fibrillation ensues.

By stimulating a discrete point on the ventricle with a brief electrical shock it is possible to estimate the susceptibility of the ventricles to fibrillation in terms of the voltage or current strength necessary to evoke an accelerating series of ectopic discharges leading to fibrillation. The dimensions of the electrical shock necessary to cause fibrillation are referred to as the fibrillation threshold.[26] Wiggers and co-workers[27] determined the fibrillation thresholds before and after coronary occlusion and found the threshold to be markedly decreased in ischemic areas. This observation throws some light on the reason for the incidence of fibrillation after coronary occlusion and directs attention toward methods of decreasing the susceptibility of the ventricles to fibrillation.

It is important to note that the fibrillation threshold can be modified by numerous drugs. Smith and associates[28] studied the effects of quinidine sulfate on ventricular activity and mortality rate following coronary occlusion and found that quinidine did not abolish the ventricular tachycardia which so often precedes spontaneous fibrillation. Quinidine did, however, materially reduce the incidence of mortality due to this cause. Wegria and Nickerson[29] studied the action of quinidine in respect to fibrillation threshold and found that ventricles protected by quinidine were more resistant to fibrillation. Quinidine apparently exerts a protecting effect by increasing the refractoriness of the myocardium.

Papaverine hydrochloride markedly increases the fibrillation threshold[29] and materially reduces the mortality rate, as demonstrated by McEachern and co-workers.[9] Lindner and Katz[30] also showed that papaverine decreases the ease with which ventricular fibrillation can be induced in the dog heart and suggested that the lessened susceptibility to fibrillation might be due in part to an increased fibrillation threshold. This drug has been shown to reduce the incidence of ectopic stimuli after coronary occlusion.[31] Since ventricular fibrillation is initiated by a series of discharges from an ectopic center,[22] it follows that the result of depressing such ectopic centers would greatly decrease the chances of sudden cardiac death. It is probable that papaverine acts to reduce the mortality rate by decreasing the excitability of the myocardium as evidenced by the reduction in the number of ectopic stimuli. Papaverine (and other drugs) may, through its vasodilator action, reduce the area of the primary infarct and thus reduce the boundary area which produces the ectopic stimuli. Whether the action of papaverine is prompt enough to do this quickly after a sudden coronary occlusion is unknown, although statistical studies indicate that over a long period of time the drug will reduce the size of the infarct.[32]

Considering these facts, we may venture to offer an interpretation of the results of Manning and associates[2,3] and those of LeRoy and associates.[4] When ventricular fibrillation occurs as a terminal event after coronary occlusion, it is frequently *preceded* by a decrease in aortic pressure. This observation has been made by Manning and associates,[2] Orias,[33] Harris,[34] and ourselves (Experiment 5). Spontaneous ventricular fibrillation in such cases does not appear until the heart has failed as a pump. The fall in aortic pressure may be due to either of two causes. First, it may occur as a result of a series of extrasystoles which do not effectively eject blood from the ventricles, or, second, the aortic pressure may decrease because of cardiac decompensation. The result of a decrease in aortic pressure due to ineffective extrasystoles or cardiac decompensation is a reduction in coronary flow and generalized myocardial ischemia which, in turn, increases the excitability of the myocardium and produces new loci of ectopic discharges. This sequence of events accounts for the darkening of the ventricular myocardium just preceding fibrillation which was correctly observed by LeRoy and co-workers[4] but erroneously interpreted as a sign of coronary vasoconstriction.[1]

Drugs, such as papaverine, which reduce the mortality rate following coronary occlusion, apparently act primarily by reducing the excitability of the myocardium as evidenced by fewer ectopic discharges. As pointed out before, the locus of the ectopic discharges is the boundary zone of the original ischemic area. Therefore, it is not necessary to postulate a reflex coronary vasoconstriction to account for their presence. An additional beneficial effect of the coronary vasodilator drugs, but one which we would relegate to a secondary role, is to increase the coronary flow in the nonischemic areas of the myocardium. Then, if aortic pressure decreases as the result of ineffective extrasystoles or cardiac decompensation, the coronary flow will not be diminished to the same extent as if the vessels were not dilated. Here again it is not necessary to assume a reflex coronary vasoconstriction.

McEachern and co-workers[3] observed that mean blood pressures were more stable after sympathectomy *and fewer extrasystoles were noted.* Since the dogs thus treated withstood coronary occlusion much better than normal dogs, it appears that under such conditions either the excitability of the myocardium is decreased or sympathectomized hearts decompensate less easily. Direct evidence on this point is lacking, but in view of the lack of evidence for reflex coronary vasoconstriction, further investigation along this line is indicated. It should be noted that at least one investigator failed to observe a favorable effect of sympathectomy on survival after coronary occlusion.[35]

On the basis of the considerations just discussed, it is apparent that the favorable effect of anesthesia, drugs, and operative procedures on survival following coronary occlusion can be explained without using the supposition of reflex coronary vasoconstriction. The evidence indicates that the favorable effect of such measures is brought about by reducing the excitability of the myocardium either to the extent that ectopic discharges from the boundary of the potentially infarcted area fail to establish continuous conduction circuits, or to a point where ectopic discharges are few or absent.

SUMMARY

Flow was measured in the anterior descendens or right coronary artery of dogs before and after occlusion of an adjacent coronary artery. Of the ten experiments conducted under either morphine-sodium barbital or morphine-chloralose anesthesia only two experiments showed a reduction in flow which could be attributed to coronary vasoconstriction and four experiments showed an increase in coronary flow. Analysis of these results and data from studies on myocardial electrical activity and on the mechanism of initiation and prevention of ventricular fibrillation fail to provide acceptable evidence for the interpretation that the greater mortality rate of unanesthetized dogs following coronary occlusion is due to a reflex coronary vasoconstriction. The favorable effects of anesthesia, drugs, and operative procedures on survival after coronary occlusion are better explained by their action on the excitability of the myocardium.

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THE FIRST TEN YEARS OF RHEUMATIC INFECTION IN CHILDHOOD

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AT THE Children's Hospital of Philadelphia, a register has been kept of all patients treated for rheumatic infection in the wards or outpatient department since 1922, at which time the clinic for supervision of patients with rheumatic infection or heart disease was founded by the late Dr. Horace Jenks. Follow-up studies of all patients not under direct observation were made on two previous occasions.[1] In 1946 and 1947, a third survey was made of all patients whose primary manifestation had occurred while they were residents of Philadelphia County during the years 1923 to 1937, inclusive. Although many had been followed for much longer periods, the present discussion is limited to the first ten years following the initial illness. All children in whom the diagnosis of rheumatic infection had been made were included, irrespective of the presence or absence of clinically recognizable heart disease.

Five hundred eighty-eight children comprised the total group. Of these, 266 were boys; 323, girls; 110, Negro; and 478 were white. The average age at onset was 6.9 years, with limits ranging from 17 months to 12 years. Seven were less than 2 years of age at time of onset; and nineteen, less than 3 years of age. At the end of the ten-year period 91.3 per cent of the group (537 children) had been located.

Criteria for the Diagnosis of Heart Disease.—In making the diagnosis of organic heart disease, transient findings during the acute phase were ignored. Children who at the termination of the initial attack or during subsequent follow-up examinations presented no cardiac enlargement and who showed normal heart sounds on auscultation, associated with no murmurs or with normal functional murmurs, were diagnosed as having no clinical evidence of heart disease (potential heart disease). Low-pitched systolic murmurs heard best in the pulmonic region to the left of the sternum or in the mid-precordium, usually associated with a twanging musical component, were diagnosed as functional, irrespective of their intensity or of the extent of the area over which they were heard. The diagnosis of mitral insufficiency was made in the presence of a persistent high-pitched systolic blow best heard at the apex, irrespective of the degree of trans-

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mission of this murmur to the left or of its intensity. In many instances a short mid-diastolic blow was associated with the systolic murmur. This mid-diastolic blow was best heard to the right of the apex and tended to disappear following subsidence of rheumatic infection. Aortic insufficiency was diagnosed in the presence of a diastolic blow to the left or right of the mid-sternum, the intensity of the murmur being disregarded. In the majority of cases there was definite evidence of cardiac enlargement but in some instances in which the diagnosis of mitral or aortic insufficiency was made cardiac enlargement could not be demonstrated by clinical or roentgenologic evidence. The presence of a true apical systolic or aortic diastolic murmur is probably in itself an indication of dilatation of the mitral or aortic ring with associated enlargement of the left ventricle, even though cardiac measurements are within normal limits. The diagnosis of mitral stenosis was made only in the presence of the characteristic diastolic rumble to the right of the apex, usually associated with accentuated first mitral and second pulmonic sounds.

Influence of the Type of Onset on Prognosis.—The group has been subdivided so as to determine the course of the disease over a ten-year period as it was modified by the type of initial infection (Tables I, II, and III).

Acute Primary Carditis: (Forty-four children, 7.5 per cent of the total group; average age at onset, 5.6 years; six children, less than 3 years of age at onset; four children, less than 2 years of age.) The diagnosis of acute primary carditis was made in the presence of a febrile illness of sudden onset associated with signs of acute rheumatic carditis but without involvement of the joints. In 42.5 per cent, acute abdominal pain was a prominent feature of the initial illness. The mortality was highest among these children, 30.2 per cent of whom ran a rapidly fatal course and 58 per cent of whom were dead at the end of ten years.* Regression of cardiac signs occurred in only one child. Two individuals in this group subsequently developed chorea; nineteen, polyarthritis. Mitral stenosis had made its appearance in three cases.

Insidious Carditis: (Forty-seven children, 8.1 per cent of the total group; average age at onset, 6.7 years.) A diagnosis of insidious carditis was made when valvular lesions characteristic of rheumatic heart disease were found during the first examination of a child with no known history of illness or with a history of scarcely recognized mild symptoms of ill health. When no definite information as to the initial illness could be elicited, the time of the first examination was taken as the time of onset. Chorea was noted subsequently in two of these individuals; polyarthritis, in twenty-two. In spite of the relatively mild form of onset, 38.3 per cent of these children were dead at the end of ten years. Regression of cardiac signs had occurred in four cases. Mitral stenosis had made its appearance in eight cases.

Myalgia and Joint Pains: (Forty-seven children, 8.1 per cent of the total group; average age at onset, 7.8 years.) Children with complaints of myalgia

*All percentages throughout this paper are based on the number of individuals traced at each time period.

TABLE I. OUTCOME OF RHEUMATIC INFECTION AT END OF ONE YEAR

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TYPE OF ONSET	TOTAL GROUP (NO.)	PATIENTS TRACED (NO.)	% OF TOTAL GROUP TRACED	% WITH RHEUM. H.D.	DEATHS				SURVIVORS		
					RHEUM.		BACT. END. (NO.)	UNRELATED (NO.)	TOTAL NO.	RHEUM. H.D.	
					NO.	%				NO.	%
Acute carditis	44	43	99.9	100.0	12	27.9	1	0	30	30	100.0
Insidious carditis	47	47	100.0	100.0	2	4.3	0	0	45	45	100.0
Myalgia	343	330	96.2	58.5	31	9.4	0	2	297	160	53.9
Acute arthritis	47	45	95.7	42.2	0	0	0	0	45	19	42.2
Chorea	107	105	98.1	24.8	2	1.9	0	0	103	24	23.3
Total	588	570	96.9	57.5	47	8.1	1	2	520	278	53.4

TABLE II. OUTCOME OF RHEUMATIC INFECTION AT END OF FIVE YEARS

TYPE OF ONSET	TOTAL GROUP (NO.)	PATIENTS TRACED (NO.)	% OF TOTAL GROUP TRACED	% WITH RHEUM. H.D.	DEATHS				SURVIVORS		
					RHEUM.		BACT. END. (NO.)	UNRELATED (NO.)	TOTAL NO.	RHEUM. H.D.	
					NO.	%				NO.	%
Acute carditis	44	43	99.9	97.6	19	44.2	3	0	21	20	95.2
Insidious carditis	47	47	100.0	93.6	7	14.9	1	1	38	35	92.1
Myalgia	47	44	93.6	45.4	4	9.0	0	0	40	16	40.0
Acute arthritis	343	324	94.5	54.0	63	19.1	1	2	258	130	50.4
Chorea	107	102	95.3	39.2	4	3.9	0	2	96	36	37.5
Total	588	560	95.2	57.3	97	17.3	5	5	453	237	52.1

TABLE III. OUTCOME OF RHEUMATIC INFECTION AT END OF TEN YEARS

TYPE OF ONSET	TOTAL GROUP (NO.)	PATIENTS TRACED (NO.)	% OF TOTAL GROUP TRACED	% WITH RHEUM. H.D.	DEATHS				SURVIVORS		
					RHEUM.		BACT. END. (NO.)	UNRELATED (NO.)	TOTAL NO.	RHEUM. H.D.	
					NO.	%				NO.	%
Acute carditis	44	41	93.2	97.5	21	52.5	3	0	16	15	93.8
Insidious carditis	47	47	100.0	91.5	16	34.0	2	1	28	24	85.8
Myalgia	47	43	91.5	51.1	5	10.6	0	0	38	17	47.3
Acute arthritis	343	312	90.9	62.5	78	25.0	5	5	224	108	48.2
Chorea	107	95	88.8	42.1	11	11.6	2	2	80	27	33.7
Total	588	537	91.3	61.3	131	24.4	12	8	386	191	49.5

or vague joint pains not serious enough to force them to go to bed were considered rheumatic only if such pains were associated with signs of infection, such as increased sedimentation rate and leucocytosis, or with evidence of carditis. The presence of slight temperature elevation as the sole associated finding was not accepted as sufficient evidence to warrant the diagnosis of rheumatic infection. Thirty-eight per cent of this group presented signs of rheumatic heart disease when first seen; 10 per cent were dead at the end of ten years. Regression of cardiac signs had occurred in one child; in six, signs of heart disease had made their appearance during recurrences of acute rheumatic infection. Nine individuals developed subsequent attacks of chorea; nineteen, polyarthritis. Mitral stenosis had made its appearance in eight cases.

Chorea: (One hundred seven children, 19.6 per cent of the total group; average age at onset, 7.6 years; one child less than 3 years of age at onset.) The diagnosis of chorea was made only in the presence of the triad of emotionalism, hypotonia of muscles, and gross incoordinate movements of an abnormal nature. After recovery from the initial illness, clinical signs of valvular heart disease were present in twenty-two children (20.5 per cent). There were no deaths due to the initial attack of chorea, but two children developed polyarthritis with fatal rheumatic carditis later in the course of the first year. At the end of ten years, thirteen (13.7 per cent) were dead of heart disease. Regression of cardiac signs had occurred in two cases; progression, in twenty-two. In sixteen instances, heart disease had made its appearance as a result of recognizable recurrences of rheumatic infection. In the remaining six cases, however, the murmur of mitral stenosis had appeared in the seeming absence of infection after a prolonged latent period. Twenty-three individuals developed subsequent attacks of polyarthritis. Mitral stenosis made its appearance in thirteen cases.

Acute Arthritis: (Three hundred forty-three cases, 58.1 per cent of the total group; average age at onset, 6.6 years; twelve children, less than 3 years of age at onset; three, less than 2 years.) The diagnosis of acute arthritis was made when the initial illness was associated with joint pains, fever, and prostration of a degree sufficient to require rest in bed. In thirty-four instances, only one joint was involved. Signs of valvular heart disease were present after recovery from the initial attack in 209 (61.1 per cent). Thirty-one children (9.1 per cent) had died of rheumatic infection during the course of the first year; eighty-seven (25.4 per cent) were dead at the end of ten years. Regression of cardiac signs had occurred in twenty- one individuals; progression, in twenty-three. In all but two of those individuals in whom signs of rheumatic heart disease appeared subsequent to recovery from the initial attack, carditis had made its appearance during an acute recurrence of the disease. The remaining two individuals had for many years not been under direct observation and may perhaps have forgotten or failed to recognize a recurrence. Chorea as a subsequent manifestation was noted in forty-six cases. Mitral stenosis had made its appearance in forty-two individuals.

Recurrences.—Forty per cent of the group had developed recurrences of rheumatic infection within the first two years; 58 per cent within five years; and 63 per cent within ten years.

The fact that the majority of rheumatic children will develop recurrences within the first five years after the onset of rheumatic infection is well known. Recurrences are the dominant factor in maintaining and increasing cardiac damage, as well as being the chief cause for the appearance of organic heart disease in the individual who was fortunate enough to escape noticeable cardiac damage in the initial illness.

Regression and Progression of Cardiac Signs.—Of the 537 individuals who were followed for a ten-year period, 318 (59.2 per cent) presented signs of organic heart disease after recovery from the initial illness. In thirty cases (9.4 per cent) there was subsequent disappearance of the physical signs of heart disease.

As compared with 63 per cent recurrence in the total group, recurrences had occurred in only nine (30.4 per cent) of this group in whom clinical signs of heart disease had disappeared; chorea appearing in three instances, polyarthritis with carditis in six. One hundred thirty-four (42.1 per cent) of the group with rheumatic heart disease at onset had died of rheumatic infection or bacterial endocarditis within the ten-year period.

Two hundred nineteen individuals showed no clinical evidence of heart disease at the termination of their first attack. Signs of organic heart disease subsequently made their appearance in fifty-one (23.3 per cent). In forty-three (82.3 per cent) such signs of valvular damage appeared during acute recrudescences of rheumatism. In eight persons (two of whom, however, had not been under direct observation for some years) the murmur of mitral stenosis made its appearance in the seeming absence of infection. In six of these eight individuals, chorea had been the only manifestation of rheumatic infection. Only eleven individuals (5 per cent) had died of rheumatic infection or bacterial endocarditis within the ten-year period.

Mitral stenosis was noted in seventy-four individuals (13.7 per cent of the entire group).

Deaths.—Within the ten-year period there were 131 deaths (24.4 per cent) due to rheumatic infection, twelve due to bacterial endocarditis, and eight due to unknown or unrelated causes. The average age at death (excluding those due to unrelated causes) was 9.3 years, with limits ranging from 18 months to 18 years. Of the deaths due to rheumatic infection, forty-seven (35.9 per cent) had occurred within the first year and ninety-seven (74.0 per cent) within the first five years. In childhood the first attack is by no means benign; in fact, more children die within the first year than in any succeeding year. These are the children unable to marshall their defenses against rheumatic infection, who can probably not be saved until a specific cure for the disease is forthcoming. As might be expected, the increment of deaths following onset was greatest among those who developed rheumatic valvular damage in the initial attack. Relatively few deaths occurred among those individuals who presented no clinical signs of

cardiac damage after recovery from the initial attack, irrespective of the presence or absence of the musical functional murmur of childhood.

Functional Status (Chart 1 and Table IV).—Ten years after onset of rheumatic infection, 151 (28.1 per cent) were dead, 131 of the deaths (24.4 per cent) being due to rheumatic infection, with or without associated acute infections.

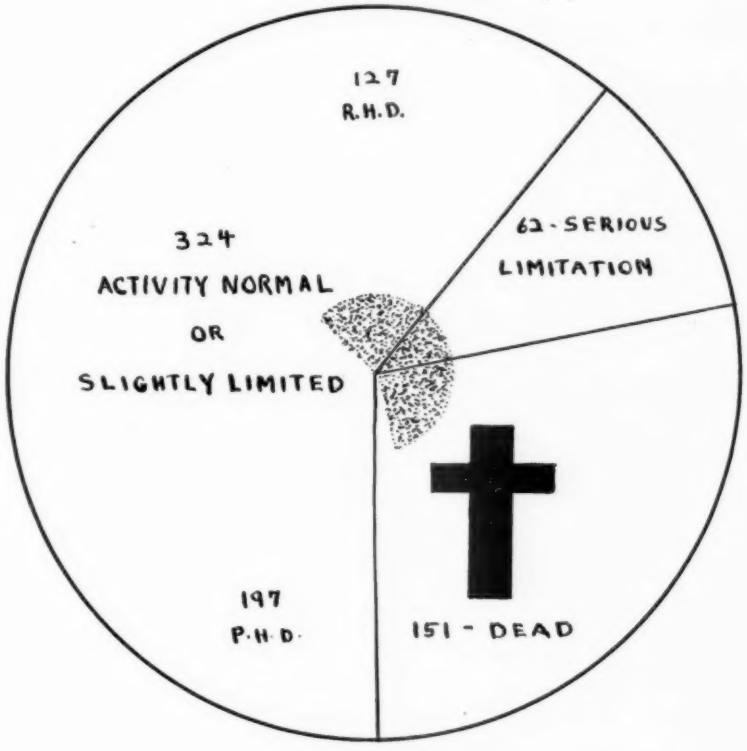

Chart 1.—Functional status of 537 rheumatic children ten years after onset. The shaded area in the center indicates the proportion of individuals in the group with rheumatic heart disease. P.H.D. = potential heart disease; R.H.D. = rheumatic heart disease.

Of the 386 survivors, 324 (60.3 per cent of the total group) were able to lead a normal life with little or no restriction of activity. Rheumatic heart disease was present in 127 of these individuals leading a normal life; potential heart disease, in one hundred ninety-seven. There was moderate limitation of activity in twenty-nine; marked limitation in eighteen. Fifteen individuals were ill with active rheumatic infection. In all of these sixty-two patients suffering from active rheumatic infection or with definite inability to lead a normal life, rheumatic heart disease was present.

A comparison of these findings with those noted by Jones and Bland in 1,000 rheumatic patients followed for ten years in Boston is presented in Table IV.

It is of interest, in view of the current theories concerning the relationship between hemolytic streptococcus infections and rheumatic fever, that only eight individuals (1.5 per cent of the total group) had suffered from hemorrhagic nephritis. Four of these attacks of nephritis occurred as isolated events bearing no relation to rheumatic infection; four occurred in association with an acute rheumatic episode. This is probably less than the incidence of hemorrhagic nephritis in the population at large.

TABLE IV. CARDIAC STATUS AFTER TEN YEARS OF RHEUMATIC INFECTION

		POTENTIAL H.D. AT ONSET		R.H.D. AT ONSET		FUNCTIONAL STATUS 10 YR. FROM ONSET		
	PATIENTS (TOTAL NO.)	NO.	% WITH P H.D. 10 YRS. AFTER ONSET	NO.	% WITH REGRESSION OF CARDIAC SIGNS 10 YR. AFTER ONSET	NORMAL ACTIVITY (% TOTAL GROUP)	P.H.D. (% TOTAL GROUP)	DEATHS (% TOTAL GROUP)
Jones and Bland[2]	1000	342	72.0	658	6.8	64.8	31.3	20.3
Ash, present series	537	219	76.7	318	9.4	60.3	36.6	24.4

R.H.D. = Rheumatic heart disease.
P.H.D. = Potential heart disease.

SUMMARY

The results of a follow-up study of 547 children who were observed for a ten-year period following the onset of rheumatic infection have been presented.

At termination of the initial attack, 59.2 per cent showed evidence of the presence of rheumatic heart disease.

Of 219 individuals with no clinical evidence of heart disease at termination of their first attack, 76.7 per cent still showed no evidence of heart disease ten years after onset. Only 5 per cent of this group with potential heart disease at onset had died of rheumatic infection or bacterial endocarditis.

Of 318 individuals with rheumatic heart disease at onset, thirty (9.4 per cent) showed disappearance of signs of cardiac involvement. Of this group with rheumatic heart disease at onset, 42.1 per cent had died of rheumatic infection or bacterial endocarditis.

The most significant prognostic factor, in so far as the initial illness is concerned, is related to the presence or absence of obvious signs of cardiac damage. Chorea at onset is relatively benign because it is less likely to be associated with carditis than is polyarthritis or other types of rheumatic infection.

Ten years after onset, 60.3 per cent of these rheumatic individuals were leading a normal existence with little or no limitation of activity. The majority of individuals presenting no functional incapacity, however, were those who

showed no clinical evidence of heart disease at the termination of the initial attack. Twenty-four and four-tenths per cent of the total group had died of rheumatic infection, the predominant number of deaths occurring among those in whom a diagnosis of rheumatic heart disease had been made following recovery from the first attack. Death had occurred in only 5 per cent of the group in whom an original diagnosis of potential heart disease had been made, in comparison with a death rate of 42 per cent among those diagnosed as having rheumatic heart disease at onset.

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ON AXIS DEVIATION IN HUMAN BUNDLE BRANCH BLOCK

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SINCE the early studies of experimental bundle branch block in the dog by Rothberger and associates,[1,2] Lewis,[3,4] and Wilson and Herrmann,[5] it has been widely believed that the development of a block in either of the main bundle branches leads to striking changes in the direction of the electrical axis of QRS as measured by Einthoven's method. Lewis[3] believed that right bundle branch block caused the electrical axis to deviate to the left, whereas a lesion of the contralateral bundle led to a deviation to the right. Wilson and his collaborators[6-11] subsequently adduced evidence that, in man, lesions of the left bundle branch were associated with left axis deviation and right bundle branch block with right axis deviation. Such axis deviation has often been assumed to be the direct consequence of the bundle branch block; we were therefore surprised to observe that when bundle branch block appeared or disappeared while the patient was under observation, there was apparently little change either in the direction of the electrical axis of QRS or in the general pattern of the electrocardiogram, apart from changes in the duration of QRS and in the T waves. This observation has not escaped previous observers, for Luten and Grove[12] and Hyman and Parsonnet[13] reported a total of seven cases, each with normal conduction and bundle branch block at different times, and remarked how little the axis deviation and general pattern of the electrocardiogram were affected by the appearance of bundle branch block. In the following study, by comparing records with bundle branch block and with normal conduction from the same patients, we have tried to ascertain the extent to which the axis deviation and the electrocardiographic pattern associated with bundle branch block are determined by the characteristics of the electrocardiogram during normal conduction.

METHODS

A complete search of over 60,000 electrocardiograms and a partial examination of 30,000 additional records revealed fifty-four cases in which there were records from the same patient with both normal conduction and typical bundle branch block. In twenty-one cases the block appeared to be in the right bundle and in thirty-three, in the left; in thirty-seven cases adequate chest leads permitted the site of the block to be determined by ascertaining on which side of the

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precordium the onset of the intrinsic deflection was delayed.[11] In the remaining cases we had to be content with judging the side of the block from the standard limb leads by the criteria advised by Wilson.[15] When adequate precordial leads were not available, cases in which the standard limb leads were not typical of one or the other type of block were excluded. In these fifty-four cases, 192 records were available, ninety showing bundle branch block only, ninety-two showing normal intraventricular conduction only, and ten records showing both bundle branch block and normal conduction in all limb leads. There were, therefore, a total of 100 instances of bundle branch block and 102 instances of normal intraventricular conduction.

Selection of Cases.—Only typical cases have been admitted to this series and the following criteria were followed:

Duration of QRS: A QRS of 0.10 second or less in normal conduction records and of 0.11 second or more in bundle branch block records was regarded as essential. In a few cases we observed a gradual increase in the QRS duration over a number of years; these cases have been excluded since they may have an origin different from that when the conduction defect appears suddenly.

P-R Interval: In order to exclude cases of Wolff-Parkinson-White syndrome, a P-R interval of 0.13 second or more has been required. In addition, a similar duration of the P-R interval in normal and in delayed intraventricular conduction records is essential to exclude ectopic ventricular rhythms as a cause of prolongation of the intraventricular conduction time. We have, however, accepted three cases of right and three of left bundle branch block in which auricular fibrillation was present, for, although we are aware that this may be open to some objection, the records were otherwise typical of bundle branch block and the ventricular rate was slow, so that an ectopic ventricular rhythm is unlikely.

Rate: To exclude temporary aberration of the QRS complexes and to exclude the majority of ectopic ventricular rhythms, only records with a ventricular rate of less than 110 per minute have been used.

Even in cases with adequate chest leads, most of these precautions are essential, since Wolff-Parkinson-White syndrome leads to premature activation of the right ventricle, and ventricular hypertrophy and ectopic ventricular rhythms may be associated with delayed activation of one or the other ventricle.

Measurement of Axis Deviation.—The axis deviation has been measured by the method of Dieuaide.[16] When the direction of the electrical axis varied with respiration, the extremes of position were measured and the average position recorded. In all cases a representative number of complexes was measured in each record. The axis deviation used in each case is an average of all available records with one type of intraventricular conduction with four stated exceptions (Table I). In these four cases, there was a progressive change of axis during the years preceding or following the development of the bundle branch block; we have, therefore, compared the axes in two successive records, one with and one without bundle branch block. Estimation of axis position from the maximum voltages of

QRS, in the traditional manner, is not a measure of the *mean* electrical axis of QRS, for this can be determined only by taking into account the duration as well as the extent of the potential changes.

TABLE I. AXIS POSITIONS IN FIFTY-FOUR CASES

CASE NO.	AXIS MEASUREMENTS (IN DEGREES)	AXIS° WITHOUT B.B.B.	AXIS° WITH B.B.B.	AXIS SHIFT WITH B.B.B.°	
				TO RIGHT	TO LEFT
L 1	−10, −3, (+44, +3) +30	+37	−3	—	40
L 2	+1, −41	+1	−41	—	42
L 6	−23, −11, −53	−17	−53	—	36
L 11	+26, +5, −18	+16	−18	—	34
L 18	−20, −20, +32, +13, −27, −16	+23	−21	—	44
L 19	−24, −47, −40	−24	−44	—	20
L 20	−14, −52, −43	−14	−47	—	33
L 21	−36, −6, +21, +7	+7	−36	—	43
L 25	−2, −30, −30, −30	−2	−30	—	28
L 28	−10, −48	−10	−48	—	38
L 32	−17, (+9, −12)	+9	−15	—	24
L 33	+4, −36	+4	−36	—	40
L 3	−10, −20	−20	−10	10	—
L 4	−29, −25	−29	−25	4	—
L 5	+44, +46, +44, +40, +43, +57	+43	+50	7	—
L 7	(−46, −48)	−46	−48	—	2
L 8	−17, −15, +3, −9, −15, −14, −20	−10	−16	—	6
L 9	−2, 0	−2	0	2	—
L 10	−25, −32, −25	−25	−29	—	4
L 12	+20, +19, +15, +42, +49	+42*	+49	7	—
L 13	−16, −11, −30, +45, +35	−16	−11*	5	—
L 14	+10, +23, +20, −9, +10, +25	+9	+21	12	—
L 15	−15, −20, −30, −30	−30	−18	12	—
L 16	−24, −19	−19	−24	—	5
L 17	−37, −10, −10, −5, −5	−10*	−10*	—	—
L 22	−30, −28	−30	−28	2	—
L 23	−21, −10, −17, −21, −17, −18, −18, −31, −13, −30	−19	−22	—	3
L 24	−22, −22, −8	−8	−22	—	14
L 26	+15, +25, +20	+20	+20	—	—
L 27	(−33, −30)	−33	−30	3	—
L 29	−10, −16, −13, −8, −11, −12, −10	−12	−10	2	—
L 30	+11, +16, +9, +9, +23, +18, +14, +20, +18, +20, +15, +20	+11	+19	8	—
L 31	(−37, −45)	−37	−45	—	8
R 1	+35, +5, +43	+20	+43	23	—
R 4	+34, +33, +32, +70	+33	+70	37	—
R 8	+54, +102	+54	+102	48	—
R 13	−14, −14, −46	−14	−46	—	32
R 14	+82, +97, +100, +95, +109, +105, +113	+82	+103	21	—
R 15	+110, +170, +140	+110	+155	45	—
R 16	−14, −36	−36	−14	22	—
R 17	+37, +97	+37	+97	60	—
R 18	(−14, +6)	−14	+6	20	—
R 19	(+43, +70) (+39, +60) (+56, +68)	+46	+66	20	—
R 2	+112, +107	+107	+112	5	—
R 3	+97, +65, +48, +37, +65, +55, +65, +63, +63, +75	+61	+64	3	—

TABLE I. AXIS POSITIONS IN FIFTY-FOUR CASES—CONT'D

CASE NO.	AXIS MEASUREMENTS (IN DEGREES)	AXIS° WITHOUT B.B.B.	AXIS° WITH B.B.B.	AXIS SHIFT WITH B.B.B.°	
				TO RIGHT	TO LEFT
R 5	*+99*, +108	+108	+99	—	9
R 6	+103, *+102*, *+97*, *+97*, *+99*	+103	+99	—	4
R 7	+140, *+148*	+140	+148	8	—
R 9	−13, *−30*, *−20*	−13	−25	—	12
R 10	*+39*, *+40*, +40	+40	+39	—	1
R 11	−40, −60, *−67*	−60*	−67	—	7
R 12	+23, *+30*	+23	+30	7	—
R 20	+143, *+135*	+143	+135	—	8
R 21	(*+152*, +138)	+138	+152	14	—

Cases developing left bundle branch block are designated "L" (thirty-three cases) and those with right bundle branch block "R" (twenty-one cases).

The figures under "Axis measurements" are given in the order in which the electrocardiograms were taken; if bundle branch block was present the figure is italicized. When both bundle branch block and normal conduction were present in the same record, the corresponding figures are bracketed.

Cases with "significant" (more than 15°) and with "insignificant" (less than 15°) shifts are grouped separately.

*Indicated cases in which all measurements have *not* been averaged, for reasons stated in the text.

Assessment of Significance of Axis Changes.—There is an inherent error in measurement of the deviation of the electrical axis of QRS due to the limited accuracy of standardization and owing to the unavoidable use of nonsynchronized records. In addition, minor changes in the position of the patient will, in some cases, alter the axis. It is difficult to assess the degree to which random changes of axis can arise from these causes, but we consider that a change of axis of less than 15° is unlikely to be of much significance. This estimate of the expected error receives some confirmation from our results, for reasons to be discussed.

Normal Range of the Position of the Electrical Axis of QRS.—For descriptive purposes it has been necessary to adopt some standard for the normal position of the electrical axis; we have used the commonly accepted range of +90° to 0° suggested by Carter, Richter, and Greene,[17] realizing that this is an arbitrary value with convenient rather than accurate limits.

RESULTS

Left Bundle Branch Block (Thirty-three Cases).—In Fig. 1, *A* we have represented the average positions of the electrical axes in thirty-three cases during normal conduction. The range of position is from +43° to −46°, the average of the positions in all cases being −6°. Twelve cases show an average axis position within normal limits, but in the remaining twenty-one cases there is abnormal left axis deviation. In Fig. 1,*B* the average positions of the electrical axes of the same cases with bundle branch block are shown; the range is from +49° to −53°, the average position being −18°; in six cases the axes are still within normal limits and in

twenty-seven cases abnormal left axis deviation is present. The appearance of left bundle branch block is, therefore, associated with a shift of the average position of the electrical axis of 12° to the left, and a change of the axis classification from normal to abnormal left in six of thirty-three cases.

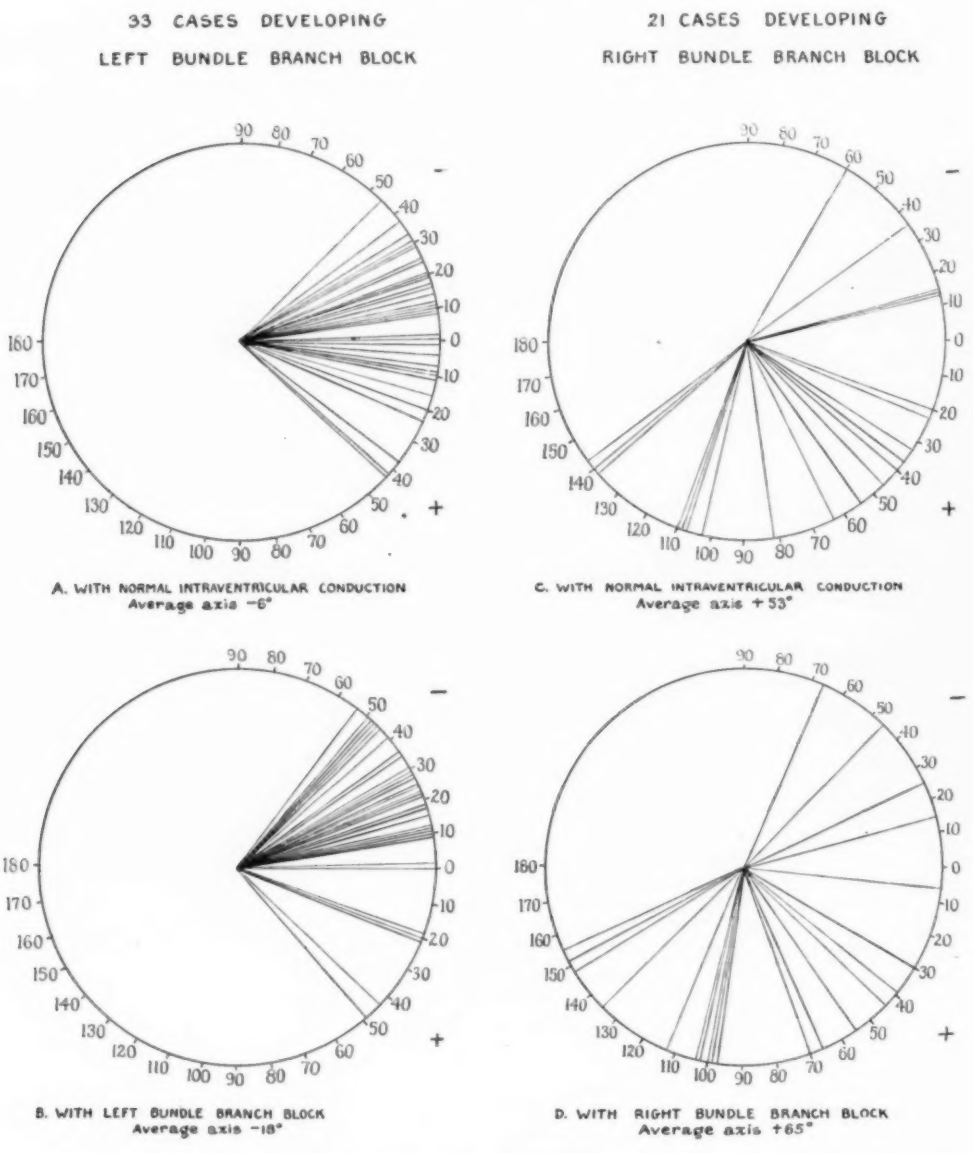
33 CASES DEVELOPING
LEFT BUNDLE BRANCH BLOCK
21 CASES DEVELOPING
RIGHT BUNDLE BRANCH BLOCK
A. WITH NORMAL INTRAVENTRICULAR CONDUCTION
Average axis −6°
C. WITH NORMAL INTRAVENTRICULAR CONDUCTION
Average axis +53°
B. WITH LEFT BUNDLE BRANCH BLOCK
Average axis −18°
D. WITH RIGHT BUNDLE BRANCH BLOCK
Average axis +65°

Fig. 1.—The average position of the electrical axis with normal conduction and with bundle branch block is represented in each case by a line at the appropriate angle; the range and distribution of the axis positions with normal conduction and with bundle branch block are thus represented, and are similar before and after the development of the intraventricular block.

If we assume that an axis shift of less than 15° is "insignificant," then a "significant" shift of axis is associated with the appearance or disappearance of left bundle branch block in only twelve of these thirty-three cases (Table I). In these twelve cases the average axis shift is 35° and the direction of the electrical axis is invariably more to the left in the presence of bundle branch block.

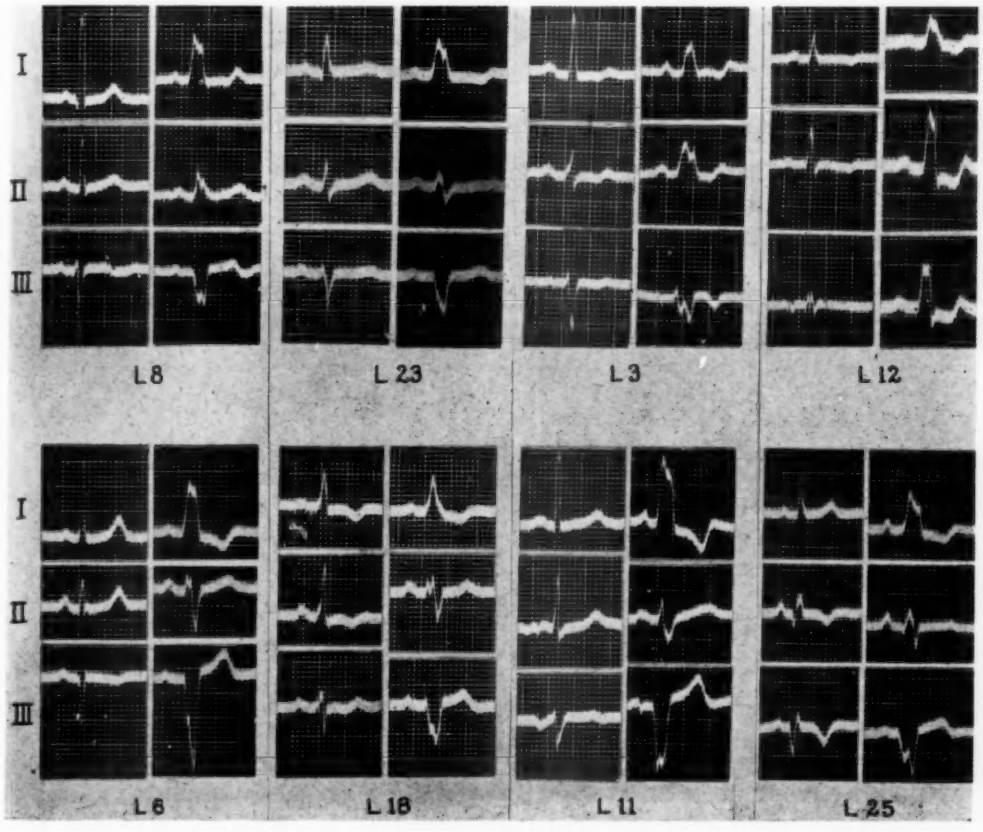

Fig. 2.—Electrocardiograms from eight cases with normal conduction and with left bundle branch block. Cases L 8, L 23, L 3, and L 12 show no significant changes of axis; the close similarity of the general pattern of the electrocardiograms with and without bundle branch block is shown, and the dependence of the concordant and discordant patterns upon the previous axis deviation is indicated on comparison of Case L 12 with Cases L 8, L 23, and L 3. Cases L 6, L 18, L 11, and L 25 show "significant" changes of axis, but the pattern of the electrocardiogram is not greatly changed; however, S waves, not previously present, appear in Lead II in Cases L 6, L 18, and L 25. The onset of the bundle branch block is associated with T-wave changes in the majority of cases.

In the twenty-one cases with "insignificant" shifts of the electrical axis when bundle branch block appeared or disappeared, there is no change in the axis in one case, in twelve cases the axis is 2° to 12° more to the right when bundle branch block is present, and in seven cases 2° to 14° more to the left (Table I). Thus, when the appearance of left bundle branch block is associated with an axis shift of 15° or more, the direction of the shift is invariably to the left, but shifts of

less than 15° are indifferently in either direction. We regard these observations as some confirmation of our opinion that an axis shift of less than 15° is of little significance and a reasonable variation in serial electrocardiograms in patients without heart disease or in whom the cardiac condition has not changed.

In Fig. 2 normal conduction and left bundle branch block records from eight patients are shown, four with and four without significant changes of axis. The electrocardiographic patterns with bundle branch block are strikingly similar to those with normal conduction.

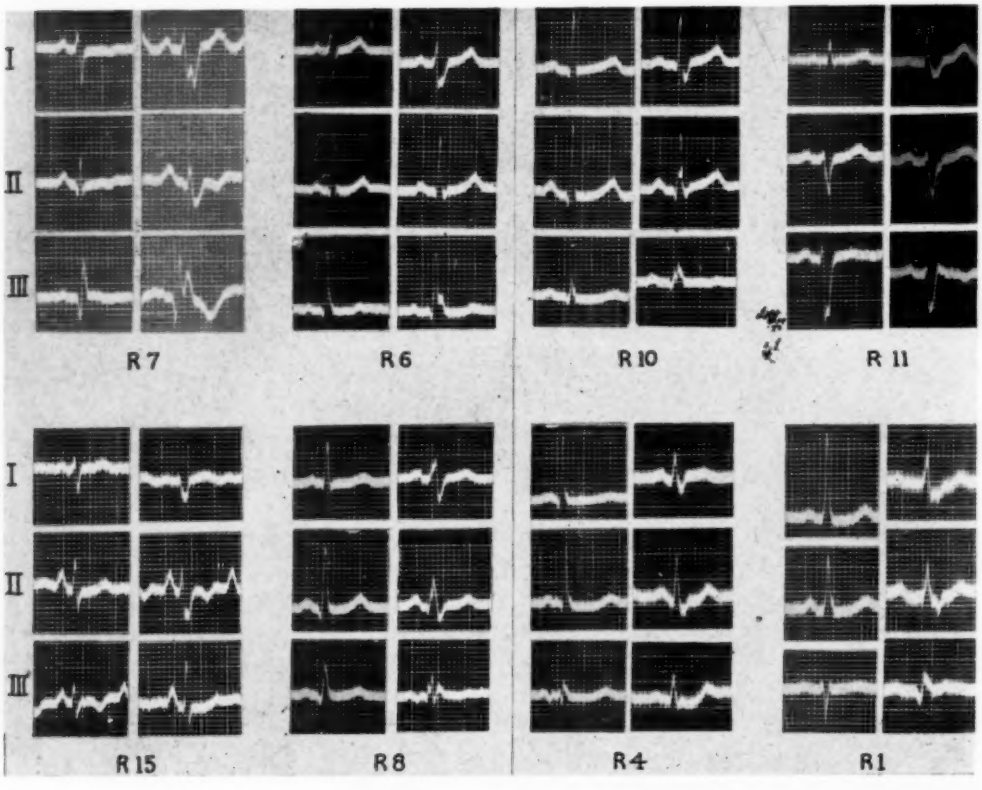

Fig. 3.—Electrocardiograms from eight cases with normal conduction and with right bundle branch block. Cases R 7, R 6, R 10, and R 11 show no significant change of axis; Cases R 7 and R 6 have abnormal right axes, Case R 10 shows normal axis position, and Case R 11, abnormal left axis deviation. The general pattern of the bundle branch block electrocardiograms closely follows that with normal conduction. Cases R 15, R 8, R 4, and R 1 show significant changes of axis, but the pattern is not greatly changed in Case R 15. The considerable changes in Cases R 8 and R 1 may be due to the anterior infarctions that occurred between the two records shown, for these would lead to decrease in the voltage of Case R 1 and a consequent shift of the axis to the right. In Cases R 8, R 4, and R 1, S waves, not previously present, appear in Lead II of the bundle branch block records. T-wave changes are less striking than in left bundle branch block (Fig. 2).

Right Bundle Branch Block (*Twenty-one Cases*).—In Fig. 1,*C* we have represented the average position of the electrical axis in our twenty-one cases during normal conduction. The range of position is from +145° to −60°, the average of

the positions in all cases being +53°; in seven cases there is abnormal right axis deviation, in nine cases the axis is within normal limits, and in five cases abnormal left axis deviation is present. Thus, in our cases developing right bundle branch block, there is a very wide range of axis position before the block appears, unlike the narrow range in our cases developing left bundle branch block. In Fig. 1,*D* the average positions of the electrical axes of the same cases with right bundle branch block are shown; the range is from +155° to −67°, the average of the positions in all cases being +65°; ten cases have abnormal right axis deviation, seven cases have electrical axes within normal limits, and in four cases left axis deviation is present. The appearance of right bundle branch block is, therefore, associated with a shift of the average position of the electrical axis of 12° to the right, and a change of the axis classification from normal to abnormal right in three cases, and from abnormal left to normal in one case.

In ten of these twenty-one cases the presence of right bundle branch block is associated with an axis shift of "significant" degree, 15° or more (Table I); in nine of these cases the axis shift is to the right and averaged 33°; in one case the axis is 32° more to the left when bundle branch block is present (Case R 13); the side of the block is not open to doubt, for characteristic chest leads were available.

In eleven of these twenty-one cases the appearance of bundle branch block is associated with only an "insignificant" shift of the electrical axis; when the block is present the axis is 3° to 14° more to the right in five cases, and 1° to 12° more to the left in six cases (Table I). As in left bundle branch block, "insignificant" shifts of the electrical axis are indifferently to the right or left, but in right bundle branch block "significant" shifts of axis are, with one exception, to the right.

In Fig. 3 normal conduction and right bundle branch block records from eight patients are shown; four without and four with "significant" shifts of the electrical axis. As in left bundle branch block, the pattern of the normal conduction record determines the pattern of the bundle branch block record.

Normal Conduction and Bundle Branch Block in the Same Record (Eight Cases).— Included in the records already considered are ten records showing both normal conduction and bundle branch block complexes in all limb leads of the same records; these ten records are from eight patients (Cases L 1, L 7, L 27, L 31, L 32, R 18, R 19, and R 21). These records merit separate consideration, for in these cases we can exclude extraneous factors such as changes in the position of the heart, cardiac infarction, or the appearance of ventricular hypertrophy as causes of a change in the position of the electrical axis between successive records with normal conduction and with bundle branch block; the errors are confined to those of axis measurement and the inaccuracy arising from the use of nonsynchronous electrocardiograms.

In four of these eight cases the shift of electrical axis is less than 15°; in two cases of left bundle branch block the axes shifted 21° and 41° to the left in the bundle branch complexes, whereas in two cases with right bundle branch block the axis is 20° more to the right in the bundle branch complexes (Table II, Figs. 4 and 5). The average shift of electrical axis was 14° to the left in left bundle

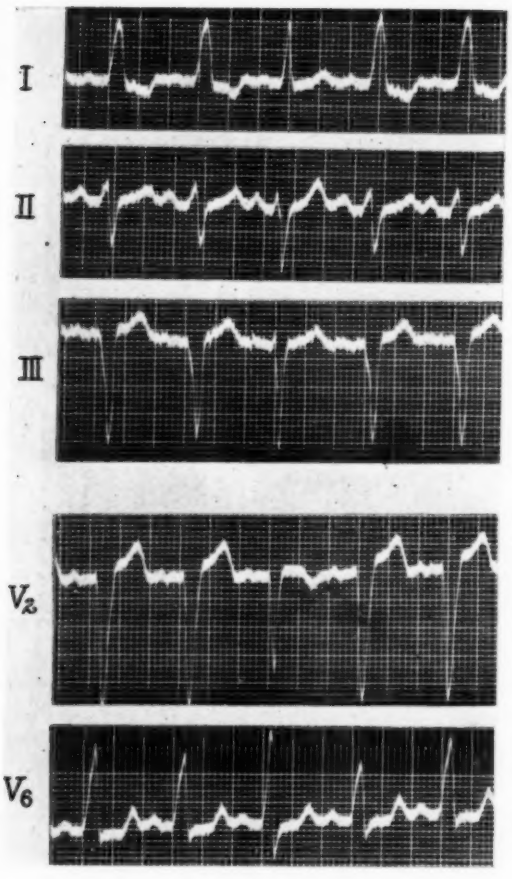

Fig. 4.—Case L 7: Normal intraventricular conduction is present in the third complex in each lead; the remaining complexes are typical of left bundle branch block. When bundle branch block is present, the longer delay in the appearance of the intrinsic deflection over the left precordium is illustrated in Lead V_6. The general pattern of the QRS complexes is comparatively little changed by the block and there is no significant shift of the electrical axis.

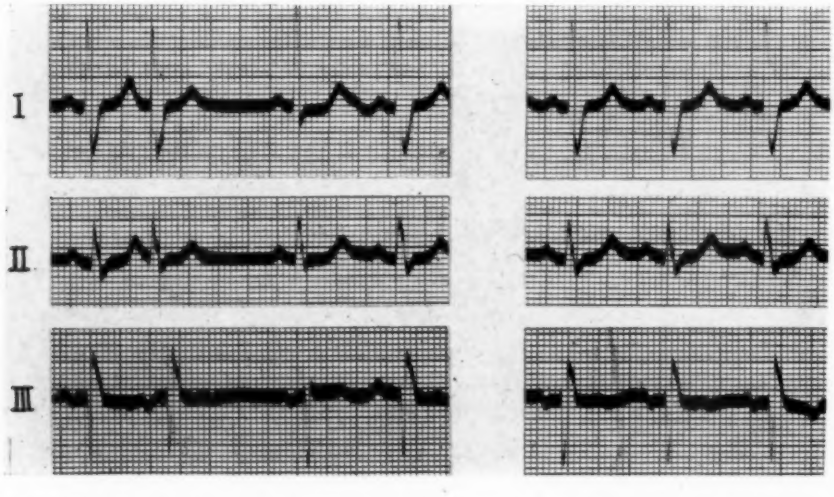

Fig. 5.—Case R 18: Normal intraventricular conduction is present in the third complex of each lead; the remaining complexes are typical of right bundle branch block. There is a change of axis of 20° to the right in the bundle branch block complexes, owing to increase in voltage of S_1 and R_3; the pattern is otherwise similar.

branch block and 18° to the right in right bundle branch block. The results in these cases, therefore, agree closely with those in the rest of our series.

TABLE II. EIGHT CASES WITH NORMAL CONDUCTION AND BUNDLE BRANCH BLOCK COMPLEXES IN THE SAME RECORD

CASE NO.	AXIS POSITION		AXIS SHIFT DUE TO B. B. B.	
	NORMAL CONDUCTION	B. B. B.	TO RIGHT	TO LEFT
L 1	+44°	+3°	—	41°
L 7	−46°	−48°	—	2°
L 27	−33°	−30°	3°	—
L 31	−37°	−45°	—	8°
L 32	+9°	−12°	—	21°
R 18	−14°	+6°	20°	—
R 19	+43° +39° +56°	+70° +60° +68°	20°	—
R 21	+138°	+152°	14°	—

DISCUSSION

Our results indicate that in these cases, (1) the range of axis positions before the appearance of bundle branch block is strikingly similar to the range when bundle branch block is present, but (2) there is an average shift of the electrical axis of 12° to the left when left bundle branch block appears and 12° to the right when right bundle branch block appears; (3) in less than one-half of our cases do we regard the axis shift as "significant," and (4) even when there is a significant shift of axis the general pattern of the electrocardiogram is not fundamentally changed by the appearance of bundle branch block. From these results we conclude that, although left bundle branch block may lead to a shift of the electrical axis to the left and right bundle branch block may lead to a shift to the right, nevertheless, this change of axis is small and comparatively unimportant in determining the axis deviation associated with the conduction lesion, which is decided principally by the position of the electrical axis before the bundle branch block appeared. It has been pointed out that we are not measuring the mean electrical axis of QRS; therefore, we cannot assume that this is similarly little affected when bundle branch block appears or disappears.

It may be considered unjustifiable to attribute to the bundle branch block the changes of axis that occurred, for factors such as a change in the position of the heart, ventricular hypertrophy, cardiac infarction, or pulmonary embolism may have developed in the interval between the two records. We believe that these factors may have played a part in a few cases; for instance, in Case R 13 (Table I) the presence of hypertension throughout the ten-year period between the last normal conduction record and the first record with right bundle branch may account for the shift of 32° to the left that was apparently associated with

the right bundle branch block. Similarly, in Cases R 1 and R 8 (Fig. 3), anterior cardiac infarction, occurring between the last record with normal conduction and the first showing right bundle branch block, may have contributed to the shift of axis to the right apparently associated with the block. But such extraneous factors can operate either to augment the change of axis or to diminish it; they may, therefore, affect the result in an individual case in either direction, but should not affect the averaged results unless the number of cases is too small or some combination of factors unusually common. In the eight cases with bundle branch block and normal ventricular conduction in the same records, we can exclude such extraneous factors; in these cases, our results have closely followed those in the whole group. We therefore consider that such extraneous factors have not played an important part in modifying the averaged results, though they ought to be taken into consideration in individual cases.

Recently, Wolferth and Livezey[18] have described five cases of right and four of left bundle branch block in which there was a rapid transition from normal conduction to bundle branch block in one or more leads. They emphasize that in these cases every effort has been made to exclude such extraneous factors as pulmonary embolism and cardiac infarction which might have affected the form of the electrocardiogram. When right bundle branch block appeared there was comparatively little change in at least the early part of QRS in the limb leads in their cases; with this observation we fully agree. Their observations on left bundle branch block were confined to four cases in which bundle branch block and normal conduction were recorded in limb and precordial leads in one case, in the three limb leads in a second case, in one limb lead in another case, and in one precordial lead (CR_1) in a fourth case. On the basis of these observations they believe that left bundle branch block "radically" affects the form of the electrocardiogram in all except the right precordial leads. One of our cases in which intermittent left bundle branch block was present is illustrated in Fig. 4; in this case neither limb nor precordial leads are strikingly changed except in the duration of QRS. In some of our cases, however, rather more striking changes were observed, but our observations on the limb leads in thirty-one and the precordial leads in twenty-four cases do not, in our opinion, justify so sweeping a conclusion as that reached by Wolferth and Livezey. Indeed, we found that, on the average, right bundle branch block led to more striking changes than left, though we doubt whether the difference is significant.

Recognition of the dependence of the axis deviation and the general pattern of the electrocardiogram in bundle branch block upon the pre-existing electrocardiographic pattern modifies the significance of any classification of bundle branch block based upon these features. Thus, Bayley[19] classified right bundle branch block, principally by the axis deviation, into four groups. In his published electrocardiograms, abnormal right axis deviation is present in cases classified in Group 1, normal axis position in Group 2, and abnormal left axis deviation in Groups 3 and 4. In Fig. 3, Cases R 3 and R 7 are examples of Group 1, Case R 10 falls into Group 2, Case R 11 into Group 4, and in Fig. 5, Case R 18 is an example of Group 3; in all these cases the pattern of the bundle branch block

electrocardiogram has been determined principally by the form of the normal conduction record. This classification of right bundle branch block, therefore, appears to be based, not upon types of bundle branch block, but upon the pre-existing form of the electrocardiogram. We believe that this opinion is not materially in conflict with Bayley's own views upon the significance of his four groups, though some of those who have subsequently used this classification have tended to attach greater significance to it. Similarly, the concordant and discordant types of curve in left bundle branch block are to be attributed to the previous electrocardiographic pattern (Fig. 2) and not to types of left bundle branch block. In our opinion, this type of classification of bundle branch block is useful solely for descriptive purposes to indicate the variety of form that may exist independently of the block, and it would be a mistake to attach any other significance to it.

When we come to consider why left bundle branch block should develop principally in patients whose original electrical axis lay in the left half of the normal range or to the left beyond the normal range, we are on less certain ground. Wilson[15] has emphasized that, in left bundle branch block, concordance or discordance of the QRS complexes depends upon the electrical position of the heart. We agree that this is an important factor in determining the axis deviation, whether or not bundle branch block is present, but we doubt whether the electrical position of the heart can explain why almost two-thirds of our cases subsequently developing left bundle branch block had abnormal left axis deviation before the block appeared. In the majority of these cases heart disease was present and it seems reasonable to attribute the axis deviation to this cause in some of these cases. Bayley[19] suggested that bundle branch block is more likely to occur in the ventricle subjected to the greater strain; if this is so it would explain why left bundle branch block often arises in patients whose electrocardiograms previously exhibited the corresponding axis deviation.

SUMMARY

Fifty-four cases with records showing both normal intraventricular conduction and bundle branch block have been collected; 192 records were available, ninety showing bundle branch block, ninety-two showing normal intraventricular conduction, and ten showing both bundle branch block and normal conduction.

The axis deviation has been measured in each record and the average position of the electrical axis of QRS during normal conduction compared with that during bundle branch block.

When right or left bundle branch block appeared or disappeared there was a significant change in the direction of the electrical axis of QRS (15° or more) in less than one-half of the cases, and the average change was 12° to the left in left bundle branch block and 12° to the right in right bundle branch block.

When a significant change of axis was associated with the appearance of bundle branch block, the direction of the change was always to the left when the block was of the left bundle branch and, except in one case, to the right when the right bundle branch was blocked.

Even in cases in which a significant change of axis was found, the general pattern of the bundle branch block electrocardiogram conformed closely to the pattern with normal intraventricular conduction.

Factors, other than the bundle branch block, that might have caused a shift of the electrical axis have been discussed; it is believed that they did not materially influence the averaged results.

It is concluded that the axis deviation and the general pattern of the electrocardiogram are not greatly modified by the appearance of bundle branch block, and that the axis deviation associated with right and left bundle branch block is due principally to the position of the electrical axis of QRS before the bundle branch block appeared.

Certain implications arising from this conclusion have been briefly discussed.

We are indebted to Dr. Crighton Bramwell, Manchester, England, for the use of the electrocardiograms in Cases L 14, R 2, and R 21. We wish to acknowledge our indebtedness to the technical staff of the Cardiographic Department, Lakeside Hospital, Cleveland, for their assistance.

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A MULTIPLE CHANNEL ELECTRONIC STETHOSCOPE FOR TEACHING AND DEMONSTRATION

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FOR many years we have been dissatisfied with our efforts at teaching the auscultatory phenomena of the human heart. We have, therefore, investigated possible means by which an entire group could listen simultaneously to a single patient, and hear the cardiac tones and murmurs as they would sound through an ordinary air conduction stethoscope.

The first attempt to accomplish this utilized a loud speaker. After considerable trial and error, this method was discarded because of technical difficulties due to feedback of the low frequencies of the cardiac sounds. Another difficulty proved to be the conditioning physicians have developed to the pressure of the stethoscope ear tips in the external auditory canals. Although accurate reproduction of the sounds could be obtained by the loud speaker, it was our experience that physicians were unable to appreciate the various tones and murmurs with this system. Any environmental noise is also a distracting factor.

We next investigated the possibility of using multiple stethophones with a special amplifier. Such an amplifier has been designed and constructed for us,* and a description follows:

The amplifier consists of four stages, the last three of which are in push-pull. Triodes are used throughout. The first, or input stage, is single-sided with high impedance input. This stage is resistance-capacity coupled to the second stage which is a duo-Triode used as a phase inverter. This feeds the third, or driver stage, which is another duo-Triode in push-pull. The fourth, or power stage, uses two 6B4G's delivering 12 watts in Class "A." Inverse feedback is used between the driver and power stages for better stability. The tone control, located in the plate circuit of the first stage, is of the base-subtractive type allowing reduction of the low frequencies. With the tone control in full base position the frequency range of the amplifier is from 40 to 5000 cycles per second. The upper cutoff is accomplished by a filter network across the output transformer. The output transformer is tapped for impedances of 2-4-8-15-250-500.

The microphone used was provided by the Cambridge Instrument Company, and is of the type used with their sound recording instruments. The output from the amplifier is led to individual jacks, wired in parallel, placed at each seat in the teaching auditorium. The students are issued individual stethophones (Monosets produced by the Telex Corporation), which are

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plugged into the jacks. Using the 2 ohm tap on the output transformer, it was found that excellent frequency response over the entire cardiac range could be obtained. There was very little volume change with one to forty or more phones in the system.

We have found that this system gives accurate reproduction of the tones and murmurs as heard through an ordinary type of stethoscope. The amplifier system was designed according to the principles outlined by Rappaport and Sprague.[1] As an additional aid in teaching, we have also used a cathode ray oscilloscope across the output of the amplifier so that the sounds heard in the stethophones may be visualized. At times we have also used a second amplifier in conjunction with the cathode ray oscilloscope so that the electrocardiogram of the patient may be visualized. In this way the image of the QRS deflection appears on the screen as a sudden sharp peak which can be used for identification of the first heart tone.

This system has several advantages. The students hear the sounds at the same time, and, therefore, it is easy for the instructor to describe and clarify any points about the tones and murmurs. Another advantage is that the student is able to sit in comfort and concentrate on listening without distracting influences. This system is also satisfying as far as patients are concerned because, as a general rule, patients dislike being individually examined by large groups of doctors. It is also a time-consuming process to allow individual examination. By the use of the tone control, tones or murmurs which are faint may be accentuated.

This system has been in use for some time and we have found from the judgment of the students, the staff of instruction, and the patients that it is by far the most workable system that we have been able to devise. It is our feeling that this, or similar types of equipment, could well be utilized by every medical school and it would be great additional aid for use in any type of meeting or conference where it would be advantageous for each individual to participate in the ausculatory examination of the heart. Auscultation of the chest is also possible. At the present time we are using forty-five stethophones in the system, but this number could be expanded to meet the needs of a group of any size.

It is possible to adapt to this purpose certain of the instruments for recording heart sounds now on the market, but we found that the expense involved would be greater, and the instrument, which is also used for electrocardiograms, must of necessity be withdrawn from routine use during periods of demonstration.

A somewhat similar system[2] has been in use on the Cardiac Division at the Philadelphia General Hospital for several years. We claim no priority, but we feel that the advantages of this type of system for instruction have never been fully emphasized.

SUMMARY

A multiple channel electronic stethoscope is described for auscultatory examination of a patient by a large group of individuals. This system has

proved to be most satisfactory for instruction. It is felt that such a system could be used to advantage by all teaching centers.

ADDENDUM

The value of this system has been greatly enhanced by adding a commercial type of recording apparatus. Recordings are made on plastic-coated records at a speed of 33 revolutions per minute. Any tones or murmurs of interest can be replayed at any time through the system without demanding the presence of the patient. It has been most useful in checking autopsy findings against the auscultatory phenomena prior to death and to keep on record for teaching such uncommon types as the Austin-Flint murmur. At present we are engaged in a long-time project of recording individual cases at frequent intervals to build a permanent record library and to develop an auditory history of the evolution of murmurs in valvular disease.

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THE DIAGNOSTIC VALUE OF THE PATTERN T_1 LOWER THAN T_3 ($T_1 < T_3$) COMPARED WITH THE INFORMATION YIELDED BY MULTIPLE CHEST LEADS IN MYOCARDIAL INFARCTION

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IN A previous report[1] the frequent association of the pattern T_1 lower than T_3 ($T_1 < T_3$) with myocardial infarction was pointed out, and the great value of this pattern for the diagnosis of infarction was emphasized. It was shown that the pattern T_1 lower than T_3 is occasionally observed with various pathologic conditions other than myocardial infarction, as, for instance, rheumatic heart disease and pulmonary emphysema, and that it may even be associated with a normal heart in vertical position. Indeed, the pattern T_1 lower than T_3 is no more specific for infarction than is inversion of T. However, in the great majority of cases it is associated with symptoms and signs of coronary disease and is equivalent to the T_1 type of myocardial infarction. When it is observed in patients who give a history suspic ous of anginal pain, it is highly suggestive of present or past infarction. It is of great diagnostic value, especially in cases in which other electrocardiographic evidence of myocardial infarction is lacking.

The presentation of the cases in the previous report[1] included only a single (apical) chest lead. Therefore, further studies were undertaken with multiple chest leads in order to ascertain the site and extent of that kind of infarction which yields the pattern T_1 lower than T_3, and also to determine the diagnostic value of this pattern as compared with the information yielded by multiple chest leads. Sixty-six cases were studied which presented the pattern T_1 lower than T_3 in association with clinical and laboratory evidence pointing to coronary disease, and, in the great majority of the cases, to myocardial infarction. From four to six chest leads were taken; in a few cases, only three or two chest leads were available. In some instances, where the customa y chest leads showed no essential change, additional leads were taken from points at a higher level in order to ascertain myocardial lesions located closer to the base of the heart. In one case, where the CR leads failed to show significant changes, a myocardial lesion was revealed by changes in the CF leads.

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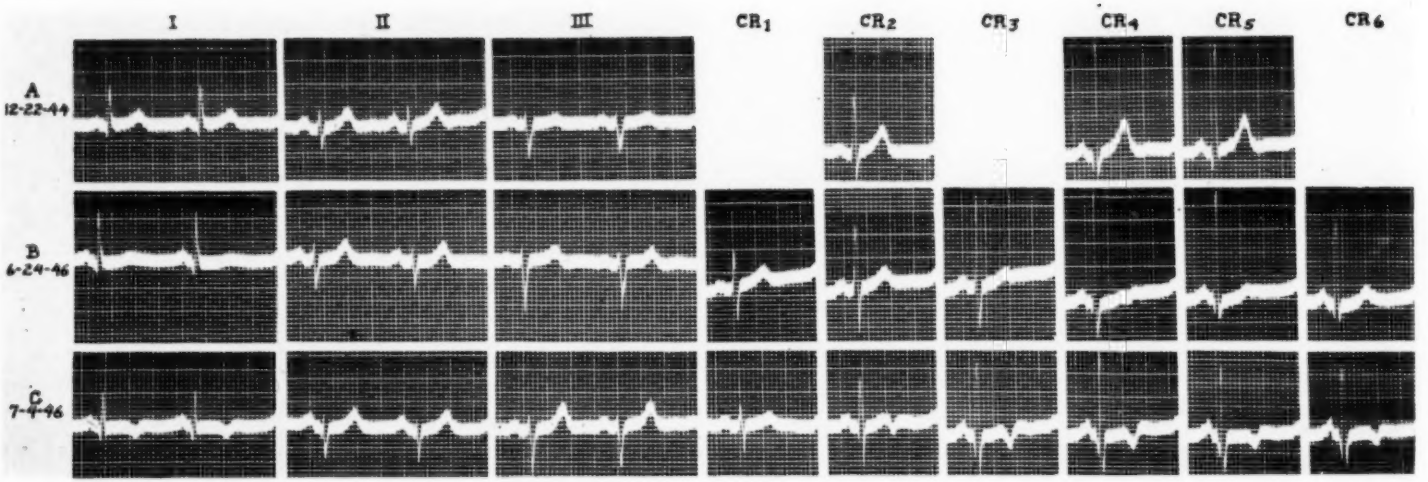

Fig. 1.—Case 1. *A*, Before the coronary attack. No significant changes in limb and chest leads. *B*, Twenty-two hours after the coronary attack. T_1 is lower than T_3. The chest leads show diminished voltage of T and, in Leads CR_3 and CR_4, partial inversion of the T wave. The changes suggest an anterior wall lesion. *C*, Eleven days after *B*. Conspicuous Q waves are present in Lead I and in chest leads from the left precordium. The T waves have become inverted in Lead I and in the chest leads, except CR_1.

CASE REPORTS

CASE 1.—A. K., a 58-year-old man, was seen for the first time on Dec. 22, 1944. He came for a routine examination and had no complaints. The electrocardiogram (Fig. 1, *A*) showed no abnormality in the limb leads or in the available chest leads (CR_2, CR_4, and CR_5). T_1 was higher than T_3.

A year and one-half later, on June 23, 1946, the patient suffered an attack of substernal pain which lasted for several hours. An electrocardiogram (Fig. 1, *B*) was obtained twenty-two hours after the onset of pain. It showed the pattern T_1 lower than T_3, which was due to decrease in the voltage of T_1 and increase in the height of T_3. In the chest leads the amplitude of the T waves was diminished and there was partial inversion of T in Leads CR_3 and CR_4. Another tracing (Fig. 1, *C*) taken eleven days after *B*, showed conspicuous Q waves in Leads I and II and in the chest leads from left precordial positions. There was inversion of T in Lead I and in all chest leads except CR_1.

Summary: The pattern T_1 lower than T_3 developed twenty-two hours after the onset of a coronary attack, before marked changes in Lead I and the chest leads appeared.

CASE 2.—B. L., a 56-year-old man, suffered an attack of severe substernal pain on July 20, 1943. This was associated with sweating and followed by a fall of blood pressure and an increase in sedimentation rate. The further course was uneventful.

An electrocardiogram (Fig. 2, *A*) was obtained on the day of the attack. In Lead I it showed a depression of the S-T junction and a diphasic (∓) T wave. In Leads II and III the T waves were of marked height. Lead CF_2 showed a QRS deflection which was mainly downwardly directed, with a rudimentary R wave. The S-T junction was elevated in Leads CF_2 and CF_3. In Lead CF_4 there was depression of the S-T segment and almost complete inversion of T.

Another electrocardiogram (Fig. 2, *B*), taken three weeks after the attack, showed progressive changes of the T waves. Significant Q waves were present in Leads CF_2 and CF_3, denoting an anteroseptal site of infarction. A third tracing (Fig. 2, *C*) was taken seven months after the coronary attack. It showed reversion of the previous changes to normal. There was slight slurring and widening of QRS. T_3 was higher than T_1; this was the only residuum of the previous coronary episode.

The patient died suddenly two and one-half years after the coronary attack. Post-mortem examination revealed an old recanalized thrombus in the anterior descending branch of the left coronary artery. An irregularly formed scar of dense connective tissue was found in the anterior wall of the left ventricle close to the septum.

Summary: Seven months after a coronary attack the pattern T_1 lower than T_3 represented the only sign of anterior infarction which was later shown by necropsy. The T waves in the anterior chest leads and in Lead I were of normal amplitude.

CASE 3.—M.G., a 45-year-old man, while driving a car in September, 1941, experienced severe substernal pain and perspired profusely. The pain lasted for only five minutes. Two days later, there was an attack of excruciating chest pain that lasted for six hours.

An electrocardiogram (Fig. 3), taken four years after the attack, was identical with a tracing obtained a day after the onset of symptoms. It showed the features of right bundle branch block. In Lead I, the S-T junction was slightly depressed and the T wave was upright and of low voltage. T_3 was much higher than T_1. In the chest leads from right precordial positions, deep Q waves were present and the intrinsic deflection arrived 0.1 second after the onset of QRS. The T waves were inverted in all chest leads. The changes were indicative of anteroseptal infarction.

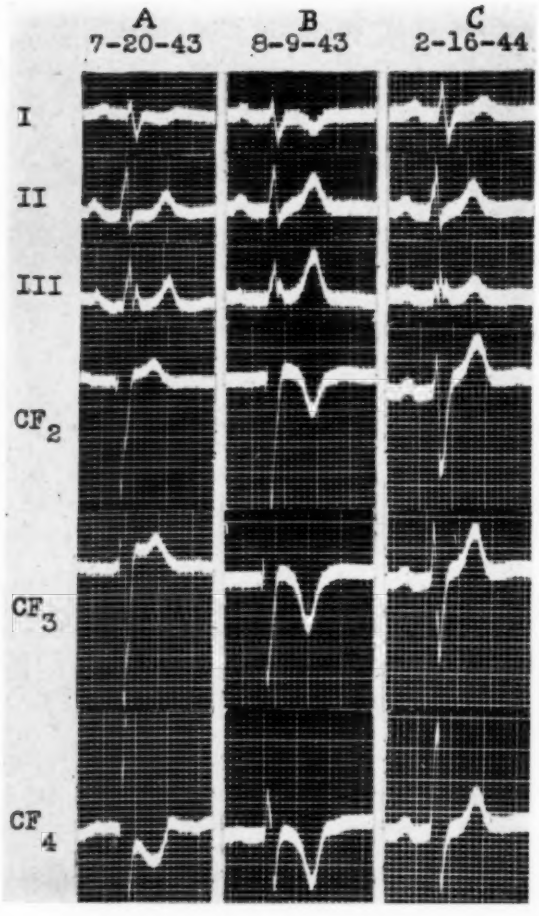

Fig. 2.—Case 2. *A*, On the day of the coronary attack. In Lead I the S-T junction is depressed and T is diphasic (∓). T_2 and T_3 are high. Lead CF_2 shows a rudimentary R deflection. The S-T junction is elevated in Leads CF_2 and CF_3 and depressed in Lead CF_4. *B*, Three weeks after the coronary attack. Significant Q waves are present in Leads CF_2 and CF_3. There is sharp inversion of T in Lead I and in the chest leads. The changes point to anteroseptal infarction. *C*, Seven months after the coronary attack. The R and T deflections have returned to normal. QRS is widened and slurred. The pattern T_1 lower than T_3 points to the old myocardial lesion. (Post-mortem examination, two and one-half years after the coronary attack, showed a dense scar in the anterior wall of the left ventricle close to the septum.)

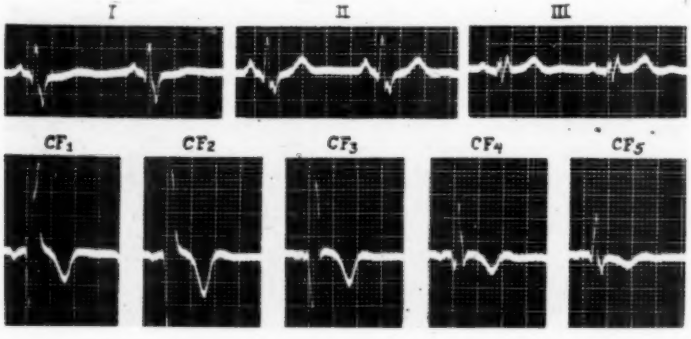

Fig. 3.—Case 3. Four years after the coronary attack. The tracing shows signs of right bundle branch block. The pattern T_1 lower than T_3 suggests an anterior wall lesion. Deep Q waves in the right precordial leads and inversion of T in all chest leads point to anteroseptal infarction.

Summary: Four years after a coronary attack the electrocardiogram showed, in the presence of right bundle branch block, the signs of anteroseptal infarction in the chest leads and the pattern T_1 lower than T_3 in the limb leads. The latter was caused by abnormal lowering of T_1 and increase in the amplitude of T_3 due to infarction. The pattern T_1 lower than T_3 is not one of the features of right bundle branch block.

CASE 4.—O. D., a 56-year-old man, had complained of mild anginal pain for the first time in July, 1945. On Aug. 3, 1945, while carrying a package, he felt severe pain across his chest which radiated to his left arm. He perspired and was nauseated. He was first examined on Aug. 7, 1945. The heart findings were normal. The blood pressure was 140/85. There was no rise in temperature. The sedimentation rate was slightly increased.

An electrocardiogram (Fig. 4, *A*), taken on Aug. 7, 1945, showed a flat T_1 and an upright T_3. Inversion of T was noted in Leads CR_2, CR_3, and CR_4.

Following the attack of Aug. 3, 1945, the patient, even when resting, experienced chest distress on several occasions, especially after breakfast. An electrocardiogram (Fig. 4, *B*), taken on Sept. 11, 1945, showed return of the T waves to normal. T_1 was higher than T_3.

The patient resumed his activities. Eight months later, on April 18, 1946, while resting, he experienced substernal pain which lasted for thirty minutes. Another milder attack occurred two days later. An electrocardiogram (Fig. 4, *C*), taken on April 22, 1946, showed the pattern T_1 lower than T_3, which was due to decrease in the voltage of T_1 and increase in the voltage of T_3. The chest leads, however, showed no abnormality. Comparison with the previous tracing (*B*) revealed that the amplitude of the T waves in chest leads from the left precordium had slightly decreased.

Summary: Two acute coronary attacks occurred within a period of eight months. After the first attack, T_1 was flat and the T waves in the chest leads were inverted. These changes returned to normal within a few weeks. The second coronary attack was indicated in the electrocardiogram only by the pattern T_1 lower than T_3, while the six chest leads failed to show significant abnormalities.

CASE 5.—M. M., a 50-year-old man, suffered an attack of substernal pain which lasted for several hours in November, 1943. It was followed by transient low-grade fever and slight rise in the sedimentation rate. The electrocardiograms for a short time showed inversion of T_3 and increased amplitude of T in Lead IV. After several weeks of rest, the patient returned to work and was free of complaints. An electrocardiogram (Fig. 5, *A*), taken on July 29, 1946, showed no abnormality. T_1 was higher than T_3.

On Oct. 22, 1946, the patient had repeated sensations of pressure in the epigastrium, lasting from ten to fifteen minutes. On the following day, he felt a "kind of indigestion" accompanied by slight pain at the lower end of the sternum; this lasted for twenty minutes. There was no rise in temperature or increase in the sedimentation rate. An electrocardiogram (Fig. 5, *B*), taken two days after the onset of symptoms, showed slight lowering of T_1 and increase in the amplitude of T_3, resulting in the pattern T_1 lower than T_3. Changes in the chest leads were inconspicuous. In Lead CF_6 there was a suggestion of a diphasic (±) T wave. Another tracing (Fig. 5, *C*), taken two days after *B*, showed more distinct changes. T_1 had become flat and the T waves in CF_6 were mainly inverted. Because of the marked changes in Lead I, it seemed advisable to explore points from higher positions on the chest, that is, three inches above Positions C_4 and C_5. These leads showed very low R waves and inversion of T. These changes suggested a high anterior (anterolateral) wall lesion.

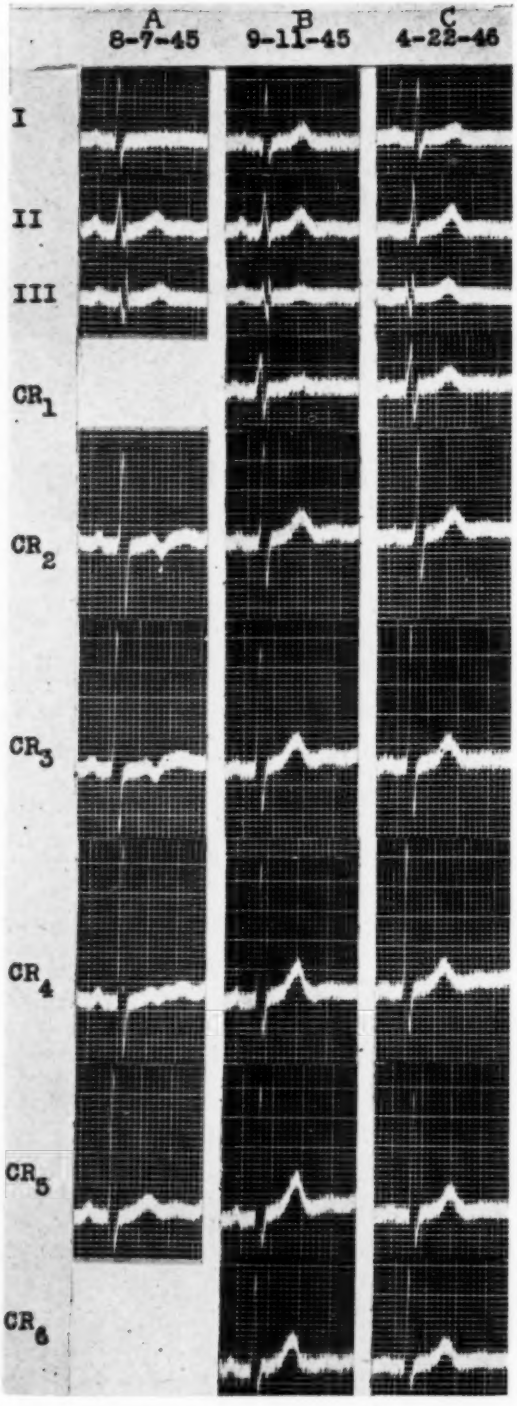

Fig. 4.—Case 4. *A*, Four days after a severe attack of effort angina. T_1 is flat; T_3 is upright. There is partial inversion of T in Leads CR_2 through CR_4. *B*, One month after *A*. The changes of T in limb and chest leads have disappeared. T_1 is higher than T_3. *C*, Four days after a mild attack of angina at rest. The limb leads show the pattern T_1 lower than T_3. The chest leads appear to be normal; only comparison with the previous tracing (*B*) reveals that the amplitude of T has slightly decreased in chest leads from the left precordium.

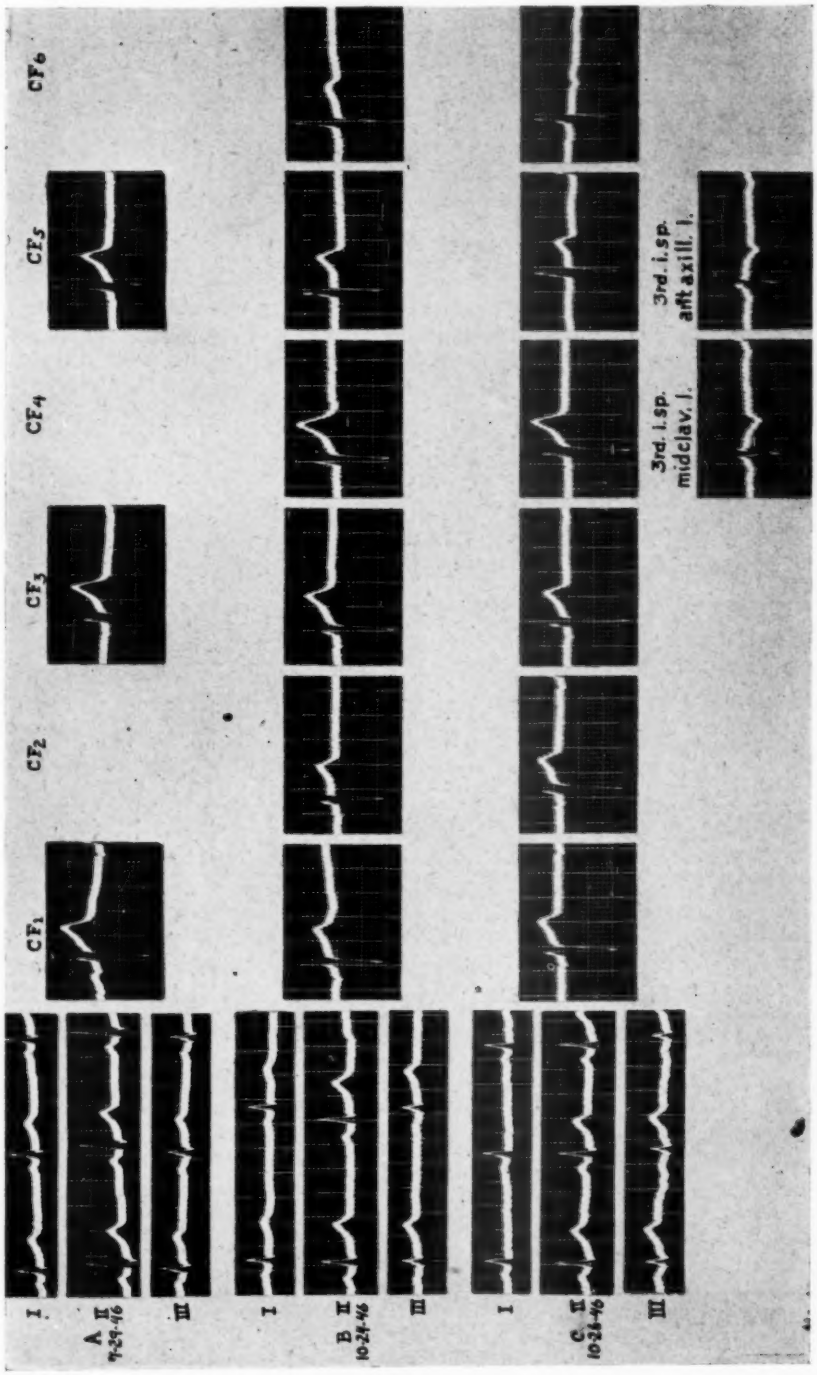

Fig. 5.—Case 5. *A*, The tracing is within normal limits. *B*, Three months after *A* and two days after onset of mild anginal attacks that recurred repeatedly during rest. T_1 is lower than T_3. In Lead CF_6 the T wave is diphasic (±). *C*, Two days after *B*. T_1 is flat. In Lead CF_6 the T wave is inverted. Tracings taken from points three inches above Positions C_4 and C_5 show low R deflections and inverted T waves. These changes suggest an anterolateral lesion located closer to the base of the heart than to the apex.

Summary: Two days after a mild coronary attack the pattern T_1 lower than T_3 developed, but changes in the customary chest leads were inconspicuous. Because of the presence of the pattern T_1 lower than T_3, points of the chest at a higher level were explored and yielded distinct changes suggestive of a high anterior (anterolateral) wall lesion.

CASE 6.—R. S., a 56-year-old man, suffered from high blood pressure. On Aug. 8, 1946, he experienced a feeling of severe substernal oppression and broke out in cold sweat. After the attack had lasted for an hour, it was terminated by an injection of morphine.

An electrocardiogram (Fig. 6, *A*), taken four days after the attack, showed the pattern T_1 lower than T_3 but no changes in the available three chest leads (CF_2, CF_4, and CF_5). The tracing was considered normal by the physician in charge and he allowed the patient to return to heavy work. Five weeks afterward, the patient was seen by one of us (W. D.), complaining of "substernal strain." An electrocardiogram (Fig. 6, *B*), taken on Sept. 14, 1946, showed T_3 still slightly higher than T_1. The chest leads from Positions C_1 through C_5 presented no abnormality, but inversion of T was present in Leads CF_6 and CF_7; this pointed to a lateral wall lesion.

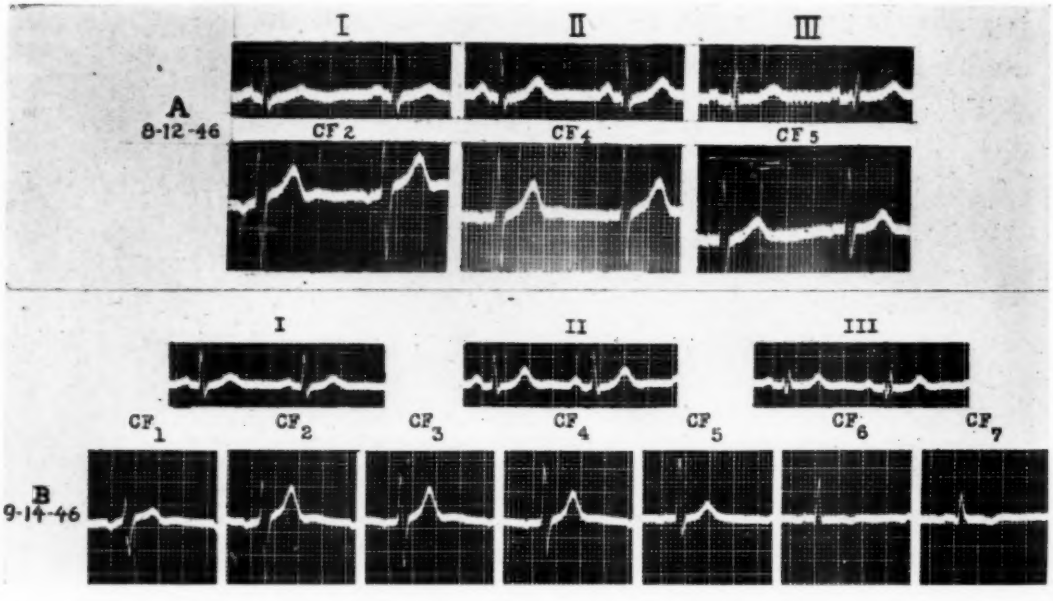

Fig. 6.—Case 6. *A*, Four days after the coronary attack. T_1 is lower than T_3. The chest leads are normal. *B*, Five weeks after the coronary attack. T_1 is slightly lower than T_3. The chest leads from Positions C_1 through C_5 are normal. Inversion of T is present in Leads CF_6 and CF_7.

Summary: Four days after a coronary attack the pattern T_1 lower than T_3 was observed while the available chest leads (CF_2, CF_4, and CF_5) showed no abnormality. An electrocardiogram taken five weeks later revealed, in addition to the pattern T_1 lower than T_3, inversion of T in leads from Positions C_6 and C_7. Leads CF_1 through CF_5 were normal.

CASE 7.—H. B. R., a 56-year-old man, was first examined on March 9, 1944, when he complained of shortness of breath in association with marked effort. Occasionally when he was excited, he would feel precordial oppression. Physical findings were negative. The blood pressure

was 120/85. Fluoroscopy showed a heart of normal size in transverse position. An electrocardiogram (Fig. 7, *A*) showed no significant abnormality. The ratio of amplitude of T_1 to T_3 was normal.

The patient was again examined on Nov. 19, 1946. He reported that one day in July, 1946, while working with a garden tractor, he had suddenly experienced pain in the upper sternal region that radiated to the left arm. The attack lasted for half an hour. Afterward, when he hurried or lifted heavy weights, he felt pain in both shoulders, in the left arm, and in the left half of his chest. An electrocardiogram (Fig. 7, *B*) showed a distinct change in the limb leads. T_1 had become slightly lower and T_3 higher than previously, yielding the pattern T_1 lower than T_3. Changes in the chest leads were inconspicuous; the amplitude of the T waves was generally less than in the previous tracing. In Lead CR_4 the T wave was a trifle lower than in the adjoining leads. Because of the presence of the pattern T_1 lower than T_3, points of the chest at a higher level were explored. They showed strikingly low T waves. An electrocardiogram (Fig. 7, *C*), taken six months later, showed a return to normal in both the limb and chest leads. T_1 was higher than T_3. In the chest leads the amplitude of T had generally increased. Especially noteworthy was the increase in the height of the T waves in leads taken three inches above Positions C_4, C_5, and C_6.

Summary: Following a mild coronary attack, the pattern T_1 lower than T_3 developed. Changes in the ordinary chest leads were inconspicuous; somewhat greater changes were observed in leads taken above the customary level. After six months, the abnormal signs in both the limb and chest leads were no longer present.

CASE 8.—G. B., a 55-year-old woman, had complained for the past year of shortness of breath in connection with effort. In October, 1944, after an argument, she experienced a band-like oppression across her chest and pain in the left elbow. After the pain had lasted for an hour, it was relieved by morphine. Physical examination of the heart revealed normal findings. The blood pressure was 110/75.

An electrocardiogram (Fig. 8) was taken two weeks after the attack. It showed the pattern T_1 lower than T_3 and an inconspicuous change in the chest leads; the T wave in Lead CR_4 was slightly lower than in the adjoining chest leads.

Summary: Two weeks after a coronary attack, the electrocardiogram presented the pattern T_1 lower than T_3; there was only an inconspicuous change in the chest leads.

CASE 9.—E. A., a 45-year-old man, early on the morning of Oct. 30, 1946, was seized with a crushing pain in the chest which radiated to his throat and both arms. It lasted for one and one-half hours. The pain recurred twice on the same day and was once followed by fainting. On the next day, there was slight rise in temperature and leucocytosis; later the sedimentation rate was increased.

An electrocardiogram (Fig. 9, *A*), taken on Oct. 31, 1946, one day after the onset of symptoms, showed in Lead I a small Q wave and an inverted T wave. In Leads II and III the T waves were high. The ordinary six chest leads showed only an inconspicuous change; the voltage of T in Lead CR_5 was slightly less than in the adjoining leads. Tracings then taken from points three inches above Positions C_5 and C_6 showed inversion of T. This suggested a lesion located closer to the base of the heart than the apex region.

The patient made an excellent recovery. An electrocardiogram (Fig. 9, *B*), taken five weeks after the coronary attack, showed an upright T_1 of low amplitude and the pattern T_1 lower than T_3. In the ordinary chest leads the T wave was again lower in Lead CR_5 than in the adjacent leads. In tracings taken from points three inches above Positions C_5 and C_6, the T waves were upright.

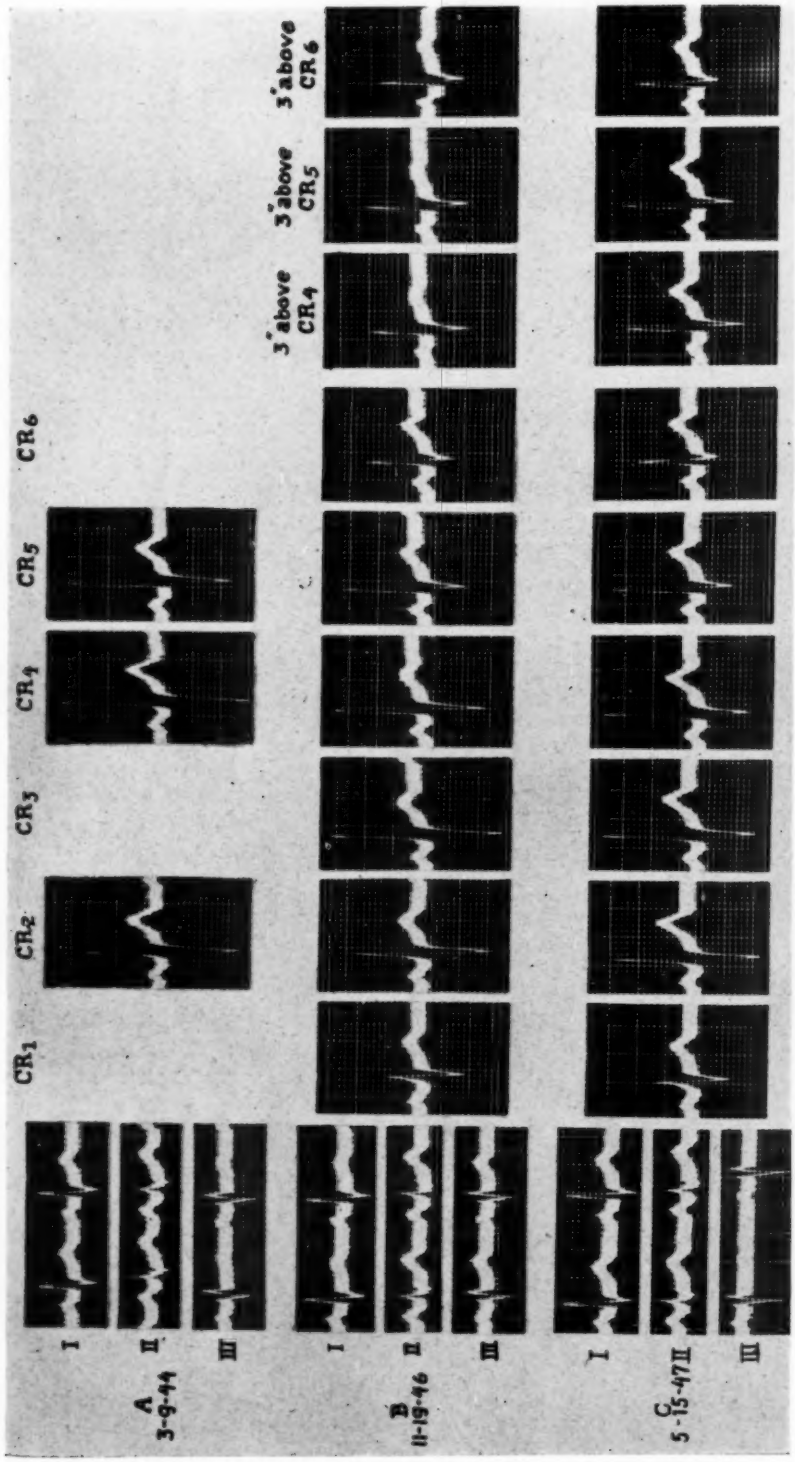

Fig. 7.—Case 7. *A*, The tracing is within normal limits. *B*, Four months after a mild coronary attack. T_1 is lower than T_3. In the chest leads the amplitude of T has slightly decreased: in Lead CR_4 the T wave is a trifle lower than in the adjoining leads. Tracings taken from points three inches above Positions C_4, C_5, and C_6 show low T waves. *C*, Six months after *B*. The pattern T_1 lower than T_3 has disappeared. In the chest leads from both ordinary and higher levels the height of T has increased, and no significant abnormality is noted.

Summary: One day after a coronary attack, the electrocardiogram showed inversion of T_1. There was only an inconspicuous change in the ordinary chest leads, but leads taken from a higher level showed inversion of T. Five weeks after the coronary attack, the inverted T waves had turned upright and the limb leads showed the pattern T_1 lower than T_3. In this case the pattern T_1 lower than T_3 reflected an infarction which was apparently located closer to the base of the heart than to the apical region.

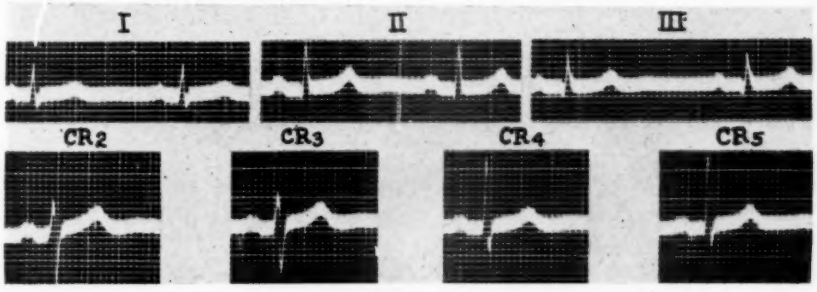

Fig. 8.—Case 8. Two weeks after a mild coronary attack. QRS is of low voltage in the limb leads. T_1 is lower than T_3. The chest leads appear to be normal except that the T wave in Lead CR_4 is slightly lower than in the adjoining leads.

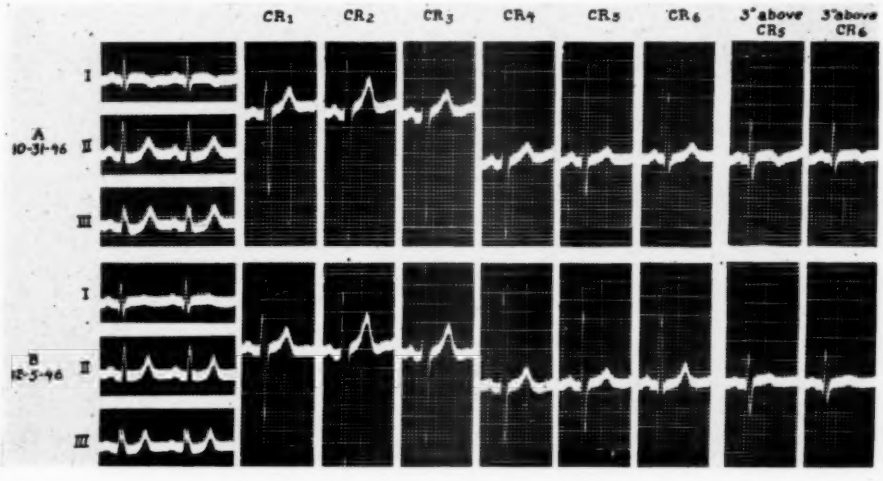

Fig. 9.—Case 9. *A*, One day after the coronary attack. T_1 is inverted. T_2 and T_3 show the features of "upright coronary T." The ordinary chest leads appear to be normal except that in Lead CR_5 the T wave is lower than in the adjoining leads. Tracings taken from points three inches above Positions C_5 and C_6 show inversion of T, closely resembling Lead I. *B*, Four weeks after the coronary attack. The T waves in Lead I and in the high chest leads have turned upright. There is the pattern T_1 lower than T_3. In the ordinary chest leads the T waves have become higher but the difference in the amplitude of T in Lead CR_5 and in the adjoining leads is even more pronounced.

Case 10.—I. S. was a 58-year-old man. Six weeks before the electrocardiogram was taken, he began to experience severe pain across the chest which radiated to the left arm when he walked two or three blocks after dinner. When he rested a short time, the pain subsided. No pain developed during rest.

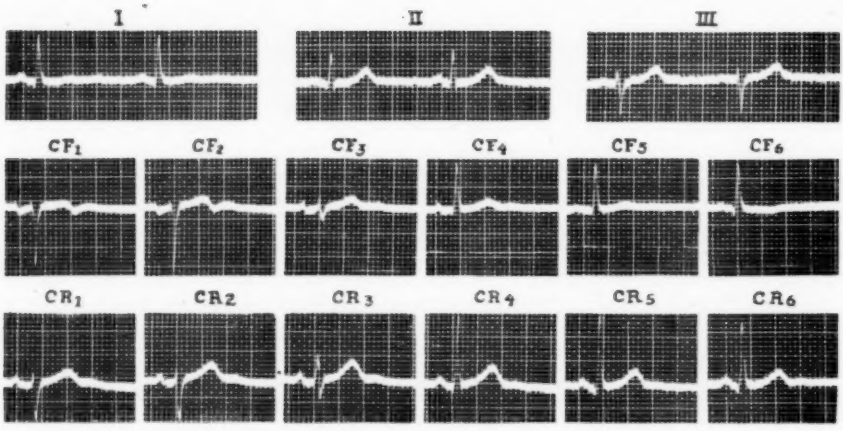

Fig. 10.—Case 10. Six weeks after sudden onset of marked angina of effort. T_1 is low; T_3 is higher than T_1. The CR leads are normal and give no clue as to the origin of the pattern T_1 lower than T_3. The CF leads, however, point to an anterior wall lesion. In Leads CF_1 and CF_2 the R deflection is low and T is diphasic (±). In Lead CF_5 the T wave is abnormally low; in CF_6 there is inversion of T.

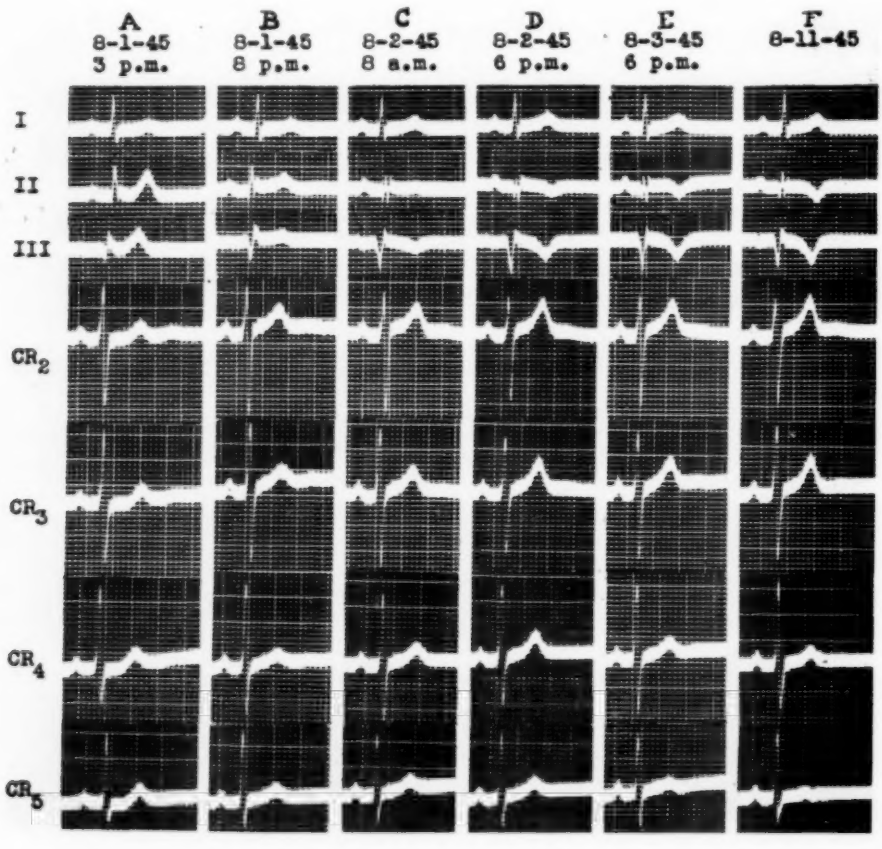

Fig. 11.—Case 11. *A*, Two and one-half hours after onset of the coronary attack. T_1 is low and T_3 is unusually high, forming the pattern T_1 lower than T_3. The chest leads show slight depression of S-T. *B*, Seven hours after onset of attack. The amplitude of T_3 has decreased. Q_3 is deeper. The deviations of S-T have disappeared. *C*, Nineteen hours after onset of attack. Significant Q waves are present in Leads II and III. T_3 is inverted. *D*, Twenty-nine hours after onset of attack. The pattern Q_2T_2, Q_3T_3 of posterior infarction is fully developed. *E* and *F*, Two days and ten days, respectively, after the coronary attack. In Lead CR_5 the T wave has become low and diphasic (±), possibly due to lateral extension of the posterior lesion.

The electrocardiogram (Fig. 1) showed a low T wave in Lead I and the pattern T_1 lower than T_3. While these changes were highly suggestive of a myocardial lesion, the CR leads failed to show significant deviations. The CF leads, however, showed distinct changes in leads from both the extreme right and extreme left precordial positions.

Summary: Six weeks after the onset of marked angina of effort, the electrocardiogram presented the pattern T_1 lower than T_3. Six CR leads failed to give a clue as to the origin of the changes in the limb leads, but the CF leads showed distinct abnormalities.

CASE 11.—J. T., a 47-year-old man, experienced substernal pain which lasted about five minutes on the evening of July 31, 1945, while he was at rest. On the next day he again felt substernal pain which was accompanied by belching and profuse perspiration. This time the distress lasted for three hours until it was relieved by morphine. The attack was followed by low-grade fever and increase of the sedimentation rate.

The first electrocardiogram (Fig. 11, *A*), taken two and one-half hours after onset of the attack of prolonged pain, showed in Leads II and III high T waves without significant elevation of S-T. T_1 was lower than T_3. In the chest leads there was slight depression of the S-T segment.

Seven hours after the onset of the attack (Fig. 11, *B*) a small Q appeared in Lead II and Q_3 was deeper than before. The amplitude of T_2 and T_3 was markedly reduced. The depression of S-T in the chest leads had disappeared.

Nineteen hours after the attack (Fig. 11, *C*) Q_3 had become broader and deeper. There was also a significant Q wave in Lead II. T_3 had become inverted, while the amplitude of the upright T_1 had increased. The pattern T_1 lower than T_3 was no longer present. The next tracing (Fig. 11, *D*), obtained twenty-nine hours after the onset of symptoms, showed the characteristic Q_2T_2 and Q_3T_3 pattern of fully developed posterior wall infarction. This could also be seen in subsequent records (Fig. 11, *E* and *F*) which, in addition, showed a diphasic (±) T wave in Lead CR_4. This was probably due to lateral extension of the infarction.

Summary: In a case of posterior infarction the pattern T_1 lower than T_3 was observed two and one-half hours after the onset of the attack. There was a striking initial increase in the amplitude of T_3. Inversion of T_3 was observed nineteen hours after the onset of symptoms. In this case the pattern T_1 lower than T_3, together with slight depression of S-T in the chest leads, represented the earliest change in posterior infarction. It preceded by twenty-seven hours the development of the characteristic Q_2T_2, Q_3T_3 pattern of posterior infarction.

DISCUSSION

Sixty-six cases were studied which presented the clinical picture of coronary disease and the electrocardiographic pattern T_1 lower than T_3 in the absence of inversion of the T waves in the standard leads. In thirty-five cases, myocardial infarction was indicated by electrocardiographic evidence other than the pattern T_1 lower than T_3, or by anginal distress which was followed by fever, leucocytosis, increase in sedimentation rate, and fall of blood pressure. In twenty-three cases, an acute coronary episode was suggested by sudden onset or aggravation of angina of effort or angina at rest; these symptoms were followed by the development of the pattern T_1 lower than T_3. In the remaining eight cases, where neither symptoms nor signs of an acute coronary episode could be elicited, the available clinical and electrocardiographic evidence pointed to chronic coronary insufficiency.

Multiple chest leads from right and left precordial positions were taken in all cases: in nineteen cases, four chest leads were available; in fourteen cases, five chest leads; and in twenty-seven cases, six chest leads. In four cases, only three chest leads were taken, and in a single case, only two chest leads were available. In one case seven chest leads were used; in five cases, where the chest leads from the customary level seemed to provide inadequate evidence, points at a higher level were explored. By this method more accurate information was obtained in two cases as to the site of the myocardial lesion which had been suggested by the presence of the pattern T_1 lower than T_3. In one case, where the CR leads did not show evidence of a myocardial lesion, the CF leads revealed definite pathologic changes.

The pattern T_1 lower than T_3 in the great majority of cases is equivalent to the T_1 type of anterior wall infarction. It was also observed in a single case of posterior wall infarction two and one-half hours after the onset of the coronary attack. In that instance, it was associated with an early increase in the amplitude of T_3 prior to the development of significant Q waves and inverted T waves in Leads II and III, which appeared twenty-seven hours after the onset of symptoms.

In the remaining sixty-five cases, the site of the lesion could be approximately determined in fifty-six patients who showed significant changes of QRS or T in multiple chest leads. In forty cases, an anteroseptal site was diagnosed; in fifteen cases, an anterolateral location; and in one instance, a posterolateral site of the myocardial lesion was suggested by the electrocardiographic changes. In nine cases, significant changes of the chest leads were not observed.

The pattern T_1 lower than T_3 occurred in both the early and late stages of myocardial infarction. In twelve cases it developed within twenty-four hours of the onset of the coronary attack. It was sometimes preceded or followed by inversion of T_1; in nine cases it represented the only electrocardiographic change. In half of the cases the pattern T_1 lower than T_3 persisted for more than a year after the acute coronary attack; in some instances it was observed as late as from four to eight years after the acute coronary episode. After such a long interval the memory of the initial attack may have faded and this possibly explains why a history of an acute coronary episode was not obtained in eight of the cases.

A previous study[1] showed that the pattern T_1 lower than T_3 is not often associated with extensive myocardial damage. This view has been confirmed by the present investigation. Significant changes of QRS, such as are associated with massive nec osis, were observed in twenty-eight cases. In twenty-nine cases the electrocardiographic changes consisted only of inversion of T, and in nine instances there was no other abnormality than reversal of the normal ratio of amplitude of T in Leads I and III. Changes of the T waves without significant changes of QRS are usually not considered as signs of serious cardiac impairment.[2] The clinical course in the cases of this study led to similar conclusions. There was not a single fatality which followed closely upon the acute coronary episode. Also, prolonged attacks of severe chest distress with cold perspiration and shock were rarely observed. In more than 60 per cent of the

cases, the acute coronary episode was marked by short attacks of angina at rest or by sudden onset or aggravation of angina of effort. Such symptoms are probably sometimes due to incomplete occlusion of a coronary branch; they may or may not be followed by a classical attack with the earmarks of massive infarction.

It has been pointed out previously[1] that the pattern T_1 lower than T_3 is not a specific sign of myocardial infarction or coronary disease. It is no more specific than is inversion of T_1. It is occasionally observed in patients with normal hearts which are vertical in position and in patients with pulmonary emphysema. These conditions in particular should be ruled out prior to diagnostic evaluation of the pattern T_1 lower than T_3. In the great majority of pathologic cases this pattern is equivalent to the T_1 type of myocardial infarction. When a history of sudden onset or aggravation of anginal pain is obtained, the finding of the pattern T_1 lower than T_3 should strongly suggest an acute coronary episode. This rule holds true even when the pattern T_1 lower than T_3 is associated with left axis deviation or with signs of right bundle branch block; it is not valid when left bundle branch block is present. Experience has convinced us that even equal amplitude of upright T waves in Leads I and III is very rare under normal conditions and should, therefore, arouse suspicion.

The finding of the pattern T_1 lower than T_3 is of particular diagnostic importance in those cases where it represents the only electrocardiographic abnormality. This happened in fourteen cases of this study. In five cases of this group, significant changes of QRS and T, or inversion of T alone, preceded the development of the pattern T_1 lower than T_3 which finally represented the only electrocardiographic abnormality. In nine instances the pattern T_1 lower than T_3 was the only electrocardiographic change throughout the course of our observation. Myocardial infarction was diagnosed on the basis of classical signs in three of the fourteen cases of this group; in one case, old anteroseptal infarction was revealed by post-mortem examination. In the remaining ten cases acute coronary insufficiency was suggested by a history of sudden onset or aggravation of angina pectoris. The fourteen cases of this group are of particular interest in that the available chest leads showed either no abnormality or only inconspicuous changes such as an abrupt, slight reduction in the height of T in a single chest lead. These slight changes might have escaped our attention had it not been for the presence of the pattern T_1 lower than T_3 which stimulated a closer scrutiny of the chest leads. The electrocardiogram in the fourteen cases of this group included two chest leads from Positions (C_2 and C_4) in one instance and three chest leads from Positions (C_2, C_4, and C_5) in another instance. In six cases four chest leads were taken from Positions (C_2, C_3, C_4, and C_5), and in the remaining six cases six chest leads were available. In three of the latter cases, in addition to the ordinary six chest leads, points at a higher level were explored. The additional (higher) chest leads showed inversion of T in one instance and yielded no additional information in the other two cases.

The cases in which six chest leads failed to show distinct evidence of myocardial damage, which was suggested by the pattern T_1 lower than T_3, prove that the ratio of the amplitude of T_1 and T_3 may be a more sensitive index of

an ischemic myocardial lesion than slight changes of the T waves in Lead I, considered alone, or inconspicuous changes of the T waves in the chest leads.* This experience is at variance with the observation of Goldberger,[3] who has stated that the pattern T_1 lower than T_3, when it is due to myocardial infarction, is invariably associated with typical patterns of anterior infarction in the chest leads. The discrepancy between our experience and Goldberger's observations may be explained by the fact that our investigations included about seven times the number of infarctions reported by Goldberger which presented the pattern T_1 lower than T_3. Also, the choice of the material and the criteria used to distinguish normal from abnormal may be a factor. Hospital material, for instance, is likely to include primarily severe cases of infarction which may readily present typical changes in the limb and chest leads. Instances of incomplete coronary occlusion, which often show the pattern T_1 lower than T_3 as the only abnormality, are less likely to be admitted to hospital wards. It must also be kept in mind that in the latter cases all other cardiac findings may be normal. Thus, the significance of the pattern of T_1 lower than T_3 which occurs, for instance, as a residual change after an old coronary accident may be missed unless a painstaking history has been taken. Such a history may reveal symptoms of a previous attack of precordial distress which otherwise are either not volunteered by the patient or are reported as innocent indigestion or gall bladder pain. Reviewing hospital charts is a less dependable method of obtaining evidence of mild or even severe coronary attacks than questioning of the patient by those who investigate a problem of coronary disease. The latter method has been followed by the authors.

The question arises as to the origin of the pattern T_1 lower than T_3, which is of particular interest in those cases of myocardial infarction where the ordinary precordial leads are normal. Goldberger,[3] quoting a formula elaborated by Wilson and associates, offered the explanation that "T_1 will be less than T_3 whenever $T_{\text{left arm}}$ is negative." This formula obviously includes not only cases presenting the pattern T_1 lower than T_3 but also those which have a negative T in Lead I and, therefore, do not belong to the group under investigation. The pattern T_1 lower than T_3 can develop only when $T_{\text{right arm}}$ is more negative than $T_{\text{left arm}}$. As will be shown later, this explains the negligible frequency of the pattern in the presence of left ventricular strain. Goldberger made no attempt to explain the occurrence of the pattern T_1 lower than T_3 in those cases of myocardial infarction where the ordinary precordial leads are normal.

The potential of the left arm is usually a mixture of endocardial and epicardial potential; in normal cases the former causes negativity and the latter causes positivity of the $T_{\text{left arm}}$. The contributions from the endocardial and epicardial surfaces to the potential of the left arm vary according to the position of the heart. "Vertical" position favors transmission of cavity potential; therefore, the T wave of the left arm is frequently negative and the pattern T_1 lower than T_3 is often observed. When the heart is in "horizontal" position, the left arm reflects principally the potential coming from the surface of the ven-

*Since this paper was written, we have observed another half dozen cases of myocardial infarction which presented the pattern T_1 lower than T_3 without changes in the customary six precordial leads.

tricle, hence the T wave of the left arm is then usually upright and T_1 is higher than T_3; indeed, T_3 is often inverted when the positive potential of the left arm is greater than that of the left foot.

In the presence of anterior or posterior infarction, $T_{\text{left arm}}$ is inverted when the potential contributed from the epicardial surface is negative. An inverted T_1 results, then, when the negative potential of the left arm is greater than that of the right arm. When the relation between the potentials of the right and left arms is the reverse, the pattern T_1 lower than T_3 develops. This pattern may occur under two conditions even when the T waves in the ordinary six precordial leads are upright and within normal limits: (1) when myocardial infarction is located close to the base and fails to alter conspicuously the precordial leads taken at the customary level; and (2) when an ischemic myocardial lesion causes, in the precordial leads, only lowering of the T waves to such degree that the latter may still appear to be within normal limits. In such cases the positive potential, contributed from the left ventricular surface to the left arm, may not suffice to counterbalance the negative potential of the cavity, and the pattern T_1 lower than T_3 results. This happens when the myocardial lesion is mild or even in the presence of a major myocardial lesion either during the early progressive stage or during the regressive stage of infarction. In anterior wall infarction the pattern T_1 lower than T_3 reflects not only changes in the anterior wall but also reciprocal changes in the posterior wall which cause an increase of the amplitude of T_3.

In our experience, the pattern T_1 lower than T_3 is very rarely encountered in the presence of left ventricular strain without infarction. The reason is that left ventricular strain, while it produces inversion of T in leads from the left side of the precordium and in Lead V_L, tends to cause the T wave of V_R to turn upright. Therefore, an inverted rather than an upright T_1 develops. It is often difficult to distinguish the inverted T of left ventricular strain from the similar change caused by myocardial infarction in the presence of left ventricular hypertrophy. Therefore, the pattern T_1 lower than T_3 may be erroneously ascribed to left ventricular strain.[3] Absence of depression of the S-T junction in leads from the left side of the precordium and in Lead V_L, that is, in the leads usually showing inversion of T in the presence of left ventricular strain, may be helpful in distinguishing ischemic myocardial lesions from left ventricular strain.

SUMMARY

Sixty-six cases which presented the clinical picture of coronary disease and the electrocardiographic pattern T_1 lower than T_3, were studied in an effort to ascertain the diagnostic value of the pattern T_1 lower than T_3 as compared with the information yielded by multiple chest leads. In most of the cases, from four to six chest leads were taken; in some instances, also, points of the chest at a higher level were explored.

In forty cases, an anteroseptal site of infarction was indicated by changes in the chest leads; in fifteen cases, anterolateral infarction was diagnosed. The pattern T_1 lower than T_3 was also observed in a single case of posterior in-

farction in the earliest stage when T_3 was unduly high prior to inversion. In nine cases, the site of the lesion could not be determined because the chest leads failed to show significant changes.

The pattern T_1 lower than T_3 is observed in both the earliest stage of myocardial infarction and as a late sign; it may persist for many years after the acute coronary episode. It is no more specific for myocardial infarction or coronary disease than is inversion of the T wave. Among other conditions, it may be associated with pulmonary emphysema and even with a normal heart that is in vertical position. When these latter conditions have been ruled out, the pattern T_1 lower than T_3 is equivalent to the T_1 type of myocardial infarction in the great majority of cases. Whenever the pattern is observed in cases presenting a history of sudden onset or aggravation of anginal pain, it should strongly suggest an ischemic myocardial lesion.

In nine cases, the pattern T_1 lower than T_3 was the prominent electrocardiographic change throughout the course of observation, while changes in the chest leads were inconspicuous or absent. This fact indicates that the ratio of amplitude of T_1 and T_3 may be a more sensitive index of a myocardial lesion than are changes of the T waves in Lead I, considered by themselves, or slight changes of T in the chest leads. Minor lesions in the anterior wall which cause only lowering of T in the chest leads may escape recognition unless they are indicated by reversal of the normal ratio of amplitude of T in Leads I and III. Also, lesions in the anterior or lateral wall close to the base of the heart may not be demonstrable in the ordinary chest leads but are suggested by the pattern T_1 lower than T_3. The finding of this pattern may lead to further exploration of the chest and, thus, to discovery of the site of the lesion.

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FURTHER STUDIES ON THE EFFECT OF PAPAVERINE UPON THE CARDIOTOXIC LESIONS OF DIGITALIS IN THE DOG

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THE fact that toxic doses of digitalis may produce myocardial lesions in experimental animals has been emphasized in many publications.[1-3] One of us (F. A. K.[3]) has recently submitted evidence that aminophylline and theobromine sodium acetate, by virtue of their dilating effect upon the coronary arteries, are more efficient than is papaverine in preventing myocardial lesions induced by toxic doses of digitalis. Since papaverine is known to be a potent coronary dilator, we have been perplexed by these results, and this work is presented to clarify further the previously reported experiment.[3]

PROCEDURE

Six young dogs received 180 to 240 mg. of digitalis daily by intramuscular injection. The dosage was varied according to the tolerance of each animal to the drug. In addition, each dog received 180 mg. of papaverine hydrochloride three times daily by intramuscular injection.

One animal was killed at the end of sixteen days and the remaining five were killed on the thirty-eighth day. Multiple sections of the hearts were made. The tissue was fixed in formalin and stained with hematoxylin and eosin for microscopic study.

RESULTS

Microscopic examination of all heart sections revealed only minimal changes. These lesions consisted of occasional scattered, small, round cell infiltrations, fraying of muscle fibers, vacuolation of fibers, and an occasional small area of necrosis of muscle fiber.

These lesions were minimal when compared with the control group of seven animals that received digitalis alone. In this control group, which has been previously reported,[3] the myocardial changes consisted of multiple areas of cellular infiltrations, marked necrosis of muscle fibers, proliferation of fibroblasts, and extreme vacuolation of cells.

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DISCUSSION

This study indicates that when papaverine is given in large dosage it will prevent the cardiotoxic lesions of digitalis in the dog. When compared with aminophylline, as used in a previously reported experiment,[3] it is found that papaverine must be administered in a dosage much larger than is usually advocated for therapeutic purposes.[4] The present paper indicates that if papaverine is to be effective in preventing the cardiotoxic lesions of digitalis in the dog, it must be used in larger dosage than in the work previously reported.

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FALSE ABNORMALITY OF PRECORDIAL ELECTROCARDIOGRAMS DUE TO THE EFFECT OF CHANGES OF POTENTIAL AT THE REMOTE ELECTRODE

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ALTHOUGH the use of precordial leads often enables the electrocardiographer better to determine the location and extent of myocardial lesions, their employment also increases the complexity of his task and without doubt has led to an increase in the incidence of incorrect interpretations. An important factor in the misinterpretation of precordial electrocardiograms is distortion of the true precordial pattern by changes of potential which occur in the region of the remote, supposedly indifferent, electrode. Whenever a single point on the body is used as the site of the "indifferent" electrode, the precordial pattern is distorted; occasionally, the distortion is of such order that abnormality may be simulated or truly abnormal patterns masked or exaggerated.

Error due to this source is best avoided by leading from the precordium to a central terminal which is connected through resistances of 5000 ohms to the three extremities used for the standard leads; Wilson and associates, who devised this method of leading,[1] have shown that only minimal changes of potential occur at the central terminal.[2] A less satisfactory practice is to estimate (from the direction and size of the deflections in the standard leads[1]) the sign and magnitude of the changes of potential at the extremity to which the remote electrode is attached and to allow for these changes in the interpretation of the precordial electrocardiogram.

During inscription of the major deflections of the ventricular complexes of normal electrocardiograms, the potential at the right arm is negative; that at the left leg, positive. Therefore, in CR leads positive (upward) deflections are exaggerated, negative (downward) deflections are decreased or abolished; this explains the alleged superiority of CR leads in recording shifts of the S-T segment due to pericarditis. Conversely, in CF leads positive deflections are reduced, abolished, or even reversed, whereas negative deflections are exaggerated.

True abnormality of precordial electrocardiograms is most often manifested by decrease in the amplitude of upward deflections or by the presence of abnormal downward deflections (Q waves and inverted T waves). This being the case,

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abnormality is most likely to be simulated in CF leads in cases in which relatively large positive potentials are developed at the left leg. The occurrence of high positive potentials at the left leg is manifested in the standard three lead electrocardiogram by large upward deflections in Leads II and III. In such cases, CF leads may appear abnormal while leads employing the central terminal (V leads) show normal patterns.

Depending upon the position of the heart in the thorax, high positive potentials may develop at the left leg during inscription of the QRS complex, or the T wave, or both. In order to illustrate distortion of the CF leads, four electrocardiograms have been selected in which both the R and the T waves are of considerable amplitude in Leads II and III.

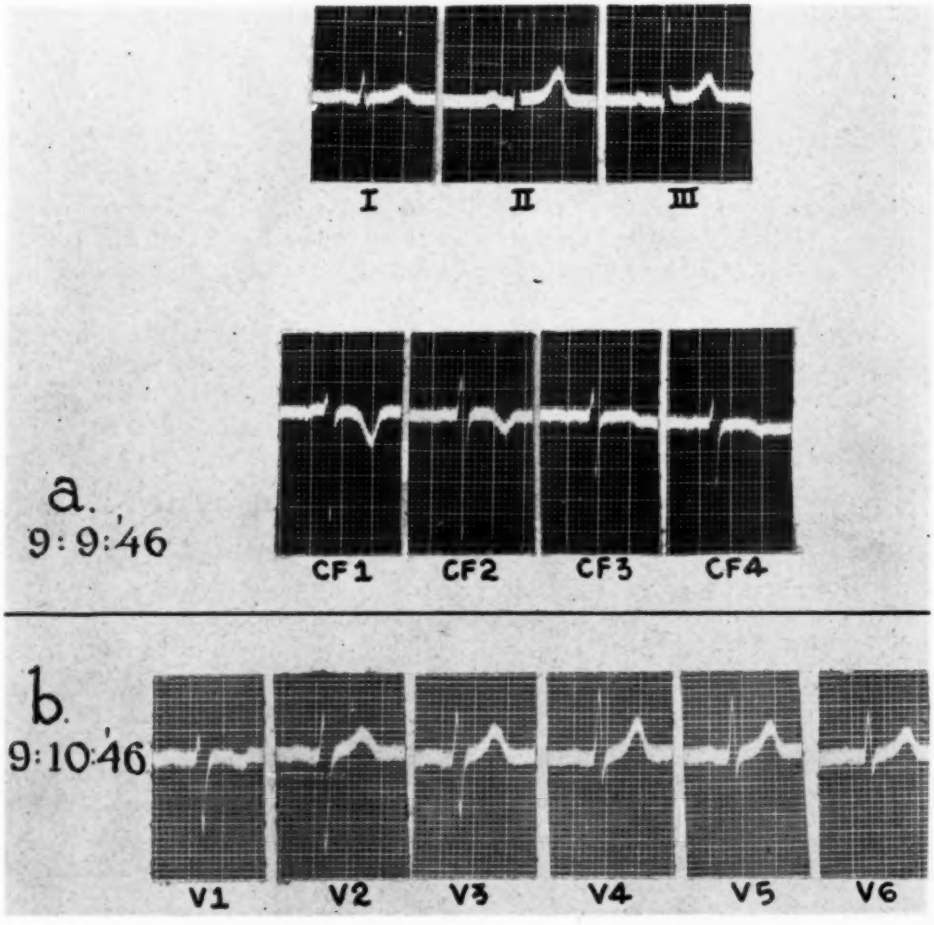

Fig. 1.—See text for explanation.

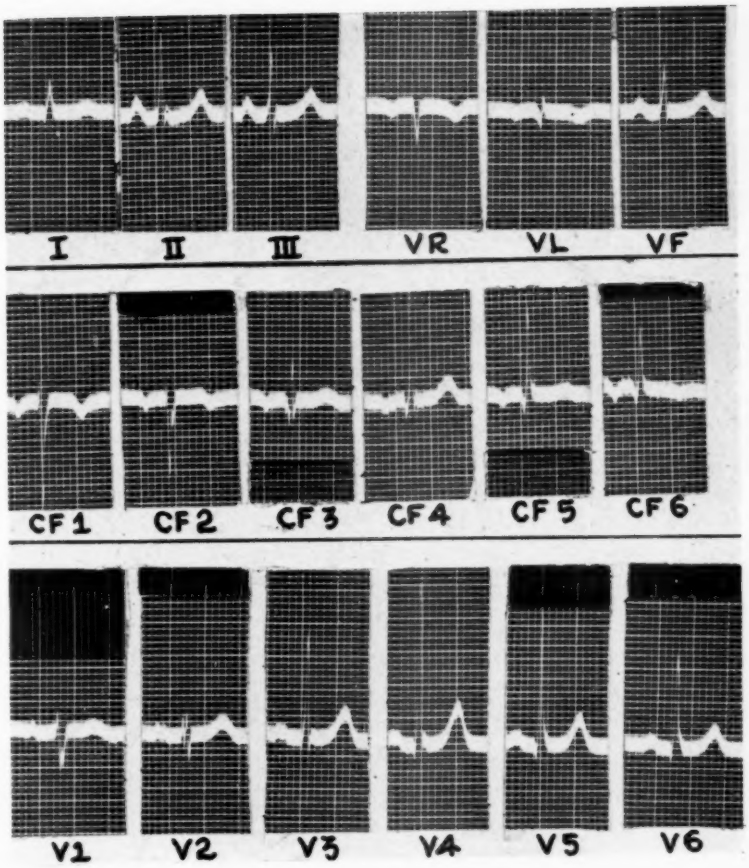

Fig. 2.—See text for explanation.

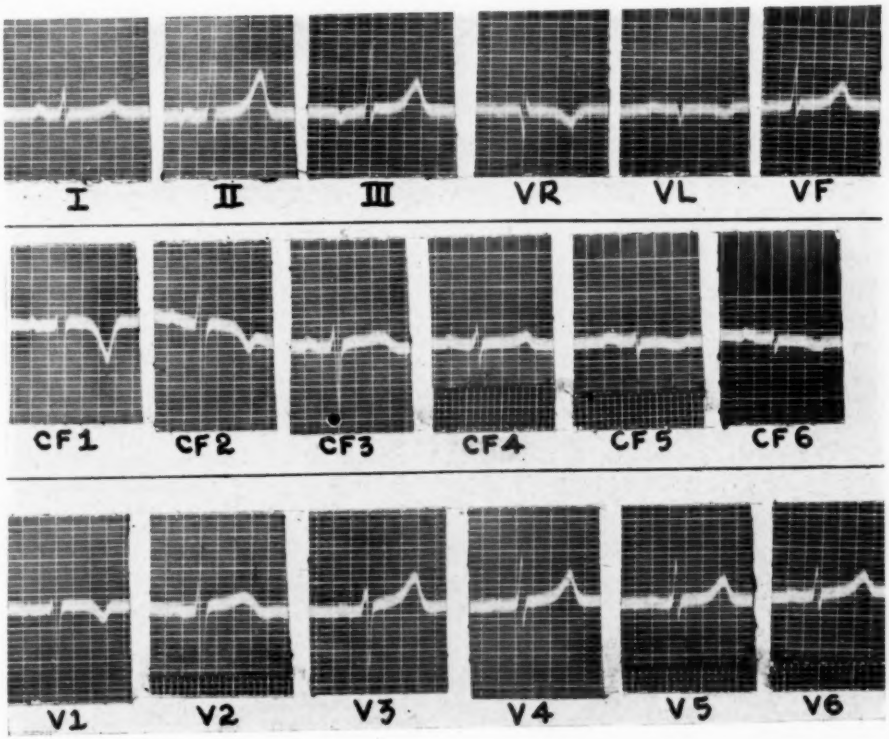

Fig. 3.—See text for explanation.

ILLUSTRATIVE ELECTROCARDIOGRAMS

The electrocardiograms of Fig. 1 are those of a white woman, 28 years of age, who on the evening of Sept. 8, 1946, after a trying day of household duties and social activity, experienced a sensation in the chest which she said felt as though she had "swallowed something that wouldn't go down." The symptom lasted about an hour, and did not recur. No signs of heart disease were detected, nor did fever, leucocytosis, or elevation of the sedimentation rate occur. On September 9, the electrocardiogram of Fig. 1,*a* was recorded, in which the T waves of the CF leads appear abnormal. In the V leads (September 10, Fig. 1,*b*), however, the T waves are normal in each precordial position. Unipolar extremity leads were not taken, but it is estimated that the maximum positive potential developed at the left leg during inscription of the T wave is nearly 0.25 millivolt.

Fig. 2 is the electrocardiogram of a thin, 68-year-old Negro man who had chronic osteomyelitis of the right femur, the sequel of an injury sustained five years before his admission to the Charity Hospital. There were no signs of heart disease; the electrocardiogram was taken as part of a general checkup prior to amputation of the diseased member. The standard leads are normal, but in Lead CF_2 the R wave is very small, and in Leads CF_2 and CF_6 the T waves are inverted. In the V leads, however, the precordial patterns are normal. The reason for the differences between the CF and the V leads is seen in the unipolar lead from the left leg (V_F), in which a positive potential of 0.6 millivolt is manifested during inscription of the QRS complex, and of 0.2 millivolt at the height of the T wave. Amputation was performed without incident, and the postoperative course was uneventful.

The electrocardiogram of Fig. 3 is that of a thin, white woman, 26 years of age, who had bronchiectasis of the right lower lobe for which lobectomy was performed on Sept. 9, 1946. The electrocardiogram was taken on September 3. No signs of heart disease were present. The standard leads are normal, but in Lead CF_2 the T wave is inverted, and in the CF leads from the left side of the precordium the amplitudes of the waves are very small; the T wave is inverted in Lead CF_6. In the V leads no abnormality is suggested. The cause of the "abnormality" of the CF leads is apparent in the V_F lead, which manifests maximum positive potentials of 0.6 and 0.3 millivolt during inscription of the R and T waves, respectively. The postoperative course was without event.

Fig. 4 is the electrocardiogram of a Negro man, 53 years of age, who had general paresis. There were no signs of heart disease; the electrocardiogram was taken as a matter of routine before the patient was given a course of fever therapy which he took without notable incident. The standard leads are normal. The T waves are inverted in Leads CF_5 and CF_6, and in the latter lead the R wave is of "abnormally" small amplitude; the V leads, however, are all normal. In this case the pattern of the QRS in all of the CF leads is rather markedly distorted by a large positive potential (1.2 millivolts at the height of the R wave) at the left leg.

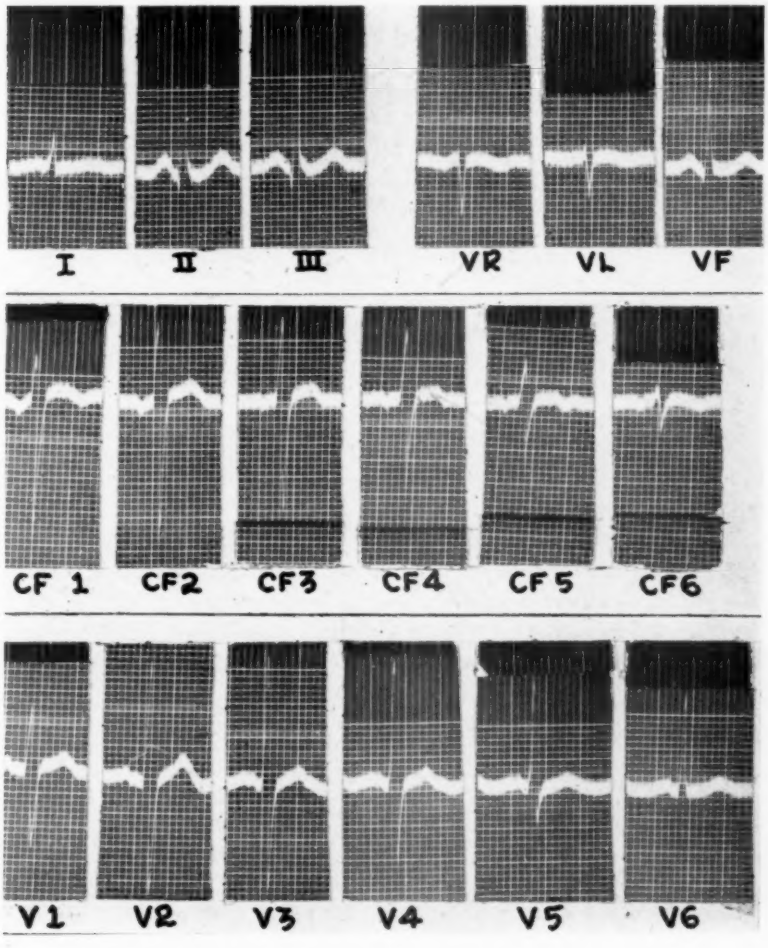

Fig. 4.—See text for explanation.

SUMMARY

Precordial leads are employed for the purpose of recording, as accurately as possible, the changes of potential that occur in the region of a single electrode placed upon the surface of the body near to the heart. This purpose is not always fulfilled, even in a practical sense, by leading from the precordium to one of the extremities. Changes of potential at the extremity may be sufficiently great to distort the precordial electrocardiogram in such a way as to simulate or to mask abnormality.

In order to emphasize this source of error in the interpretation of electrocardiograms, four normal records are reproduced, in which abnormality of the CF leads is simulated by distortion of normal precordial patterns.

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A SIMPLE METHOD OF DETERMINING ABNORMALITIES OF THE Q-T INTERVAL

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RECENT observations that the Q-T interval is significantly prolonged in rheumatic fever[1,5] have once again directed attention to the problem of measuring of the Q-T interval. Study of the interval has always been difficult because it varies with the ventricular rate; and before one can state that a measured Q-T interval is abnormal, the Q-T interval must be compared with the ideal Q-T interval that theoretically should occur with that particular ventricular rate. This, however, involves complicated formulas and calculations.[2-5]

For this reason, the following simple nomogram for calculating the relation of the Q-T interval, as measured, with the ideal Q-T interval for that particular ventricular rate was developed. It is based on Bazett's formula $Q\text{-}T = .4\sqrt{R\text{-}R}$ where R-R is the interval between two successive R waves. The relation between the measured Q-T interval and the ideal Q-T interval for that particular heart rate can be called the *Q-T ratio.*

METHOD

1. Measure a typical R-R interval. This is easily done by counting the number of thin time spaces between two successive R waves. Multiply this number by .04, because each of the thin time intervals represents .04 second.
2. Mark this value on the column, *R-R Interval Measured* (Fig. 1).
3. Measure the Q-T interval in the first of the complexes that were used to measure the R-R interval.
4. Mark this value on the column, *Q-T Interval Measured* (Fig. 1).
5. Place the straight edge of a ruler on the marks on these columns. Note where the ruler edge cuts the column, *Q-T Ratio.*

This value is the Q-T ratio. It indicates whether the Q-T interval as measured is longer (Q-T ratio values above 1) or shorter (Q-T ratio values below 1) than the ideal Q-T interval. For example, a Q-T ratio of 1.2 means that the measured Q-T interval is 120 per cent of the ideal Q-T ratio. A Q-T ratio of .95 means that the measured Q-T interval is only 95 per cent of the ideal Q-T interval for that particular heart rate.

From the Medical Division, Montefiore Hospital, New York, N. Y.
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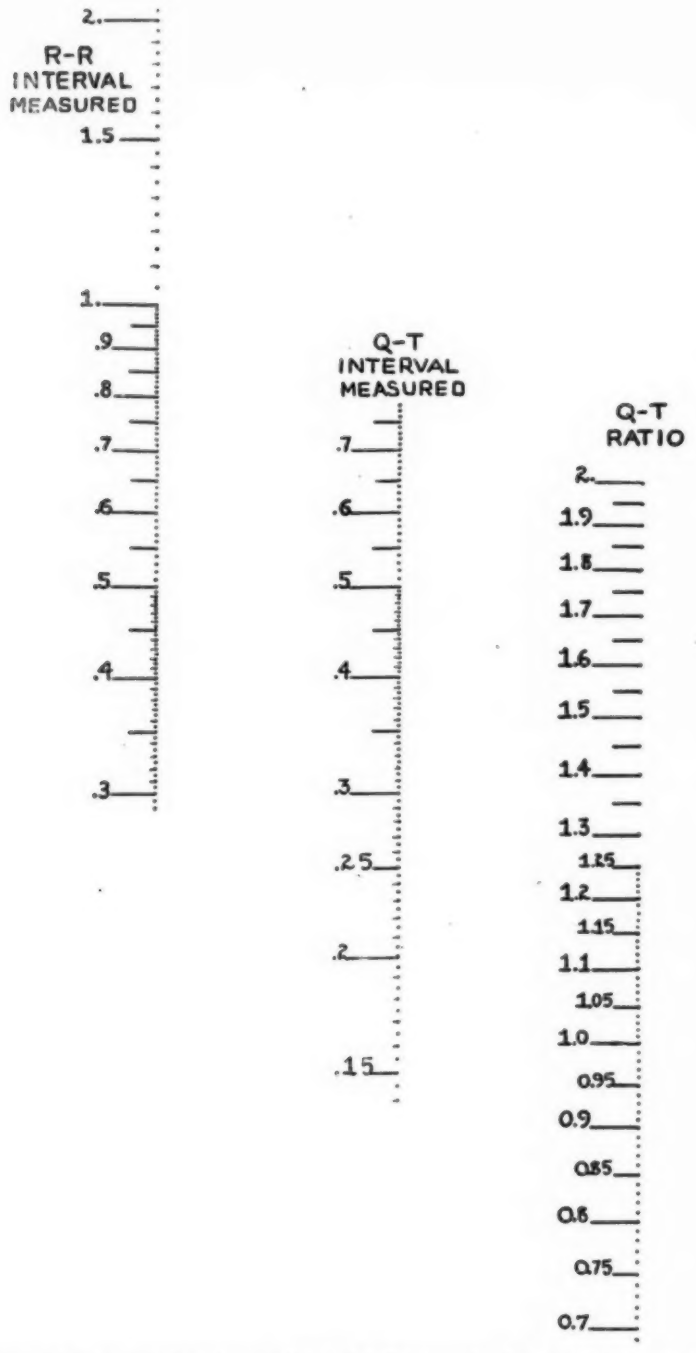

Fig. 1.—Nomogram for determining abnormalities of Q-T interval. See text for description of its use.

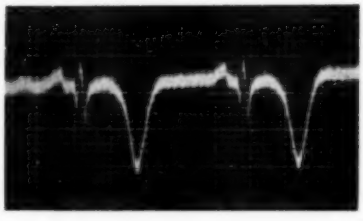

Fig. 2.—Lead CR_4. Acute anterior myocardial infarction. See text.

Example (Fig. 2): Acute anterior infarct. In Lead CR_4, R-R interval measured 0.92 second. Q-T interval measured 0.46 second. Q-T ratio is 1.20. This is abnormal. An abnormal Q-T ratio is to be expected after myocardial infarction.

DISCUSSION

The ideal Q-T interval is different for men, women, and children. Bazett[2] pointed out that it is longer in women and gave the formula $Q\text{-}T = .37\sqrt{R\text{-}R}$ for men and children, and the formula $Q\text{-}T = .4\sqrt{R\text{-}R}$ for women. However, Fenn[3] stated that the formula $Q\text{-}T = .39\sqrt{R\text{-}R}$ could be used for men and women. Recently, Ashman[5] showed that when Fenn's formula was used, many normal Q-T intervals were longer than the ideal Q-T intervals. Therefore, I used the formula $Q\text{-}T = .4\sqrt{R\text{-}R}$ in constructing the nomogram. This value corresponds with the values obtained by Taran and Szilagyi[1] in children.

Theoretically, Q-T ratio values above 1 are abnormal and less than 1 are normal. Clinically, the normal upper limit for the Q-T ratio for children is 1.01, calculated from Taran and Szilagyi's data. However, the normal Q-T ratio can be as large as 1.09 for men and children and 1.12 for women, using the normal upper limits of the Q-T interval described by Ashman and Hull.[6] No complete studies on the normal minimal values for the Q-T interval have appeared.

SUMMARY

A nomogram has been presented by which the measured Q-T interval is compared with the ideal Q-T interval expected for that particular heart rate. The result is described as the *Q-T ratio*. The Q-T ratio normally should not exceed 1.01, but values as large as 1.09 in children and men, and 1.12 in women can occur normally.

The author wishes to express his appreciation to Max Shiffman, Ph.D., Associate Professor of Mathematics, New York University, for his help in constructing the nomogram.

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Clinical Reports

HIGH VENTRICULAR SEPTAL DEFECT WITH SLIGHT DEXTROPOSITION OF THE AORTA (EISENMENGER TYPE) WHICH PRESENTED THE CLINICAL FEATURES OF PATENT DUCTUS ARTERIOSUS

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THE case which will be presented serves to emphasize that the exact differential diagnosis of congenital heart disease is often not as simple as clearly stated clinical criteria[1,7] would lead one to believe. This has become quite apparent as more and more cases of congenital heart disease now undergo surgery for the relief of pulmonary stenosis and patent ductus arteriosus. Recent communications[2-4,6,7] indicate to what extent the old criteria may fall short, and suggest that right heart catheterization may lessen the number of errors in diagnosis. In operations for patent ductus arteriosus, for example, the errors in diagnosis stand at 2.6 per cent in 643 cases up to January, 1947.[5]

CASE REPORT

The family physician had informed the mother of P. S. that congenital heart disease was present when the patient, P.S., was 10 months of age; this was reaffirmed when she was 3 years of age. From 1941 on, greater activity resulted in increasing difficulties until her death in January, 1947, at the age of 21 years. The patient was married and deserted in her eighteenth year and was remarried and had a pregnancy interrupted in her nineteenth year. Her care was complicated by her subnormal mental and economic status. During intercurrent infections, which were sometimes prolonged and accompanied by fever, leucocytosis, and an elevated sedimentation rate, no evidence was found to support suspicion of subacute bacterial endocarditis. In spite of repeated severe epistaxis, platelet counts and bleeding time determinations were normal.

In 1941, at the age of 16 years, her dyspnea and the violent action of her heart on moderate exertion were painfully evident to her mother. The only striking features of her general examination were her mild mental retardation and a mongoloid expression with an extremely wide interorbital space. There was moderate pallor but no cyanosis. The heart was grossly enlarged, as evidenced by the area of cardiac dullness which reached almost to the anterior axillary line and by the visible and palpable systolic thrust. A systolic-diastolic thrill was palpable over the whole precordium; it was of greatest intensity over the pulmonic valve area. No intensification of the thrill was noted over the aortic valve area. The auscultatory findings included a harsh systolic basal murmur transmitted

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far laterally in both directions, which blended into a loud diastolic murmur which completely filled diastole. In the second intercostal space to the left of the mid-sternal line, this machinery-like murmur was most intense.* The systolic element of this continuous murmur was heard clearly over the left chest posteriorly. No distinguishable separate murmurs could be heard over the aortic valve area at this time and none were heard over the neck vessels. The blood pressure was 90/50. The electrocardiogram showed a sinus rhythm, with a rate of 70 per minute; the P-R interval was 0.20 second, QRS measured 0.10 second in duration, and there was terminal inversion of T_3, T_2 and T_4 being abnormally large. There was no evidence of either right or left axis deviation. Anteroposterior and lateral x-ray films of the chest showed gross increase in heart size with increase in the shadow of both the right and left sides of the heart; the shadow of the pulmonary conus was very prominent and that of the aortic knob relatively small. The bronchovascular markings were definitely increased. It was felt that the presence of a patent ductus arteriosus was more likely than the presence of a defect of the interventricular septum or incomplete rotation of the great vessels.

In January, 1945, when she was admitted to the hospital for the control of severe epistaxis, the to-and-fro murmur and the coarse purring thrill were felt to be more prominent and more characteristic of a patent ductus arteriosus. For the first time there was found in the aortic valve area, in the second intercostal space to the right of the sternum, a short blowing diastolic murmur which differed in quality from the diastolic murmur which had been observed in the pulmonary area. The new murmur was regarded as evidence of the development of a minor degree of aortic insufficiency. There was still no evidence of congestive failure, but the cardiac reserve was not as good as it had been in 1941. The blood pressure was recorded as 70/40.

By May of 1945, following her second marriage and overwork in a laundry, she developed early signs of congestive failure with intermittent swelling of the ankles. Râles were heard at the lung bases for the first time. The intensity of the thrill had increased. At the same time, she complained of throbbing of the pulse in her ears. On June 1, 1945, a pregnancy was interrupted and the Fallopian tubes ligated.

In November, 1945, following four weeks of low-grade respiratory infection, she was admitted to the hospital because of vomiting, with moderate fever and leucocytosis, coarse râles, and tachycardia. The vomiting had induced a puffiness of the face and resulted in the appearance of many petechial hemorrhages over the cheeks and eyelids, although a cuff test was negative. During her severe paroxysms of cough she became extremely cyanotic. This transient cyanosis with increased thoracic pressure (cyanose tardive) seemed to confirm further the impression that a patent ductus arteriosus was present.[1] She responded nicely to penicillin and rapid digitalization. Blood cultures were negative.

In July, 1946, she was admitted because of epistaxis. No gross signs of congestive failure were present, but over a period of eleven days she lost nine pounds of occult edema, without a mercurial diuretic, on the regime used for congestive heart failure which included an average daily fluid intake of 4500 c.c. and a low-sodium, acid-ash diet. The heart action was more violent and the murmurs and the thrill previously described were intensified. In addition to the diastolic murmur over the aortic area, first noted in January, 1945, there was now audible a short systolic murmur in the aortic area unaccompanied by a thrill, which was transmitted to the neck vessels. A pistol shot sound was heard over the femoral vessels, but Duroziez's sign was absent. The blood pressure was 130/72. The diagnosis of patent ductus arteriosus was adhered to and it was felt that minimal aortic stenosis and regurgitation had developed as a result of superimposed rheumatic endocarditis.

In December, 1946, râles were noted at the lung bases and all the previous abnormal physical signs were more striking than in July. The blood pressure was 145/80-50. An x-ray film of the chest taken on Jan. 6, 1947, seemed entirely compatible with a diagnosis of patent ductus arteriosus (Fig. 1). Fluoroscopy of the chest showed a markedly enlarged pulmonary conus and a relatively

*Abbott[1] describes the typical murmur of patent ductus as follows: A " . . . machinery murmur, beginning just after the first sound and continuous throughout the greater part of the cardiac cycle, localized over the first, second or third interspace with maximum intensity at the second, with an accompanying . . . continuous thrill, which when present is pathognomonic." The murmur is distinct from the "holosystolic harsh murmur maximum in the third or fourth left interspace" of la maladie de Roger.

small aortic knob, as well as hypertrophy of both ventricles. Pulsation in the left ventricle and pulmonary artery occurred synchronously. Hilar dance was not present, and there was no displacement of the barium-filled esophagus. While arrangements for surgical treatment were in the process of being made, during the night of Jan. 11, 1947, the patient developed extreme dyspnea and expired suddenly.

The clinical diagnosis was (1) congenital heart disease, patent ductus arteriosus. (2) Acquired rheumatic heart disease, aortic stenosis and insufficiency.

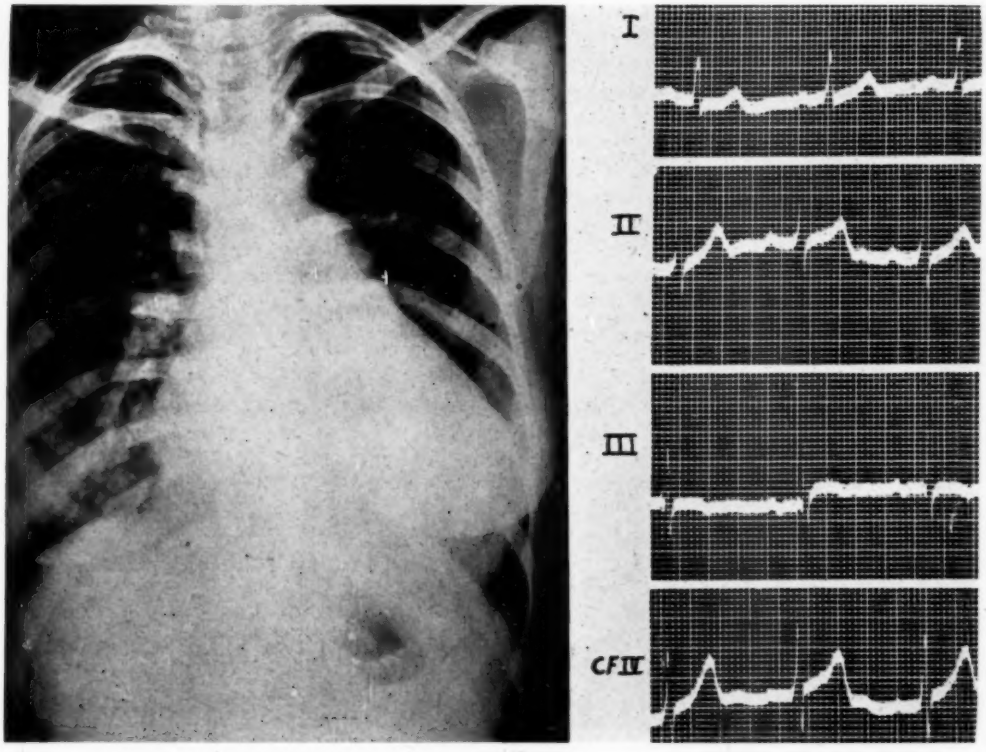

Fig. 1.—The electrocardiogram shows no right or left axis deviation. T_2 and T_4 are abnormally large. The P-R interval measures 0.20 second.

The teleroentgenogram of the chest shows the increase in size of the heart and the fullness over the area of the pulmonary artery, and an inconspicuous aortic knob. Fluoroscopy confirmed the presence of a dilated pulmonary artery which pulsated synchronously with ventricular systole. Hilar dance was not seen. Barium pursued a normal course through the esophagus.

Pathologic Findings.—The heart and lungs were removed "en bloc." The pulmonary artery was slightly dilated and the wall slightly thickened. The unopened aorta was no larger than the pulmonary artery. Careful dissection failed to disclose a patent ductus arteriosus and no ligamentum arteriosum was present.

The heart weighed 675 grams. There was a single area of epicardial fibrosis, measuring 3 by 4 mm., on the anterior surface of the right ventricle opposite the high ventricular defect which will be described. The left ventricle averaged 2.0 cm. in thickness, while the right ventricle averaged 1.0 cm. in thickness. The endocardium was smooth and glistening and the papillary muscles were hypertrophied bilaterally.

A ventricular septal defect was found to extend from the ventricular surface of the base of the mid portion of the tricuspid valve through the interventricular septum to emerge at the base of the

Fig. 2.—The right cusp of the aortic valve, thick and bucket-shaped, is drawn up gently to show its position in systole and expose the interventricular defect.

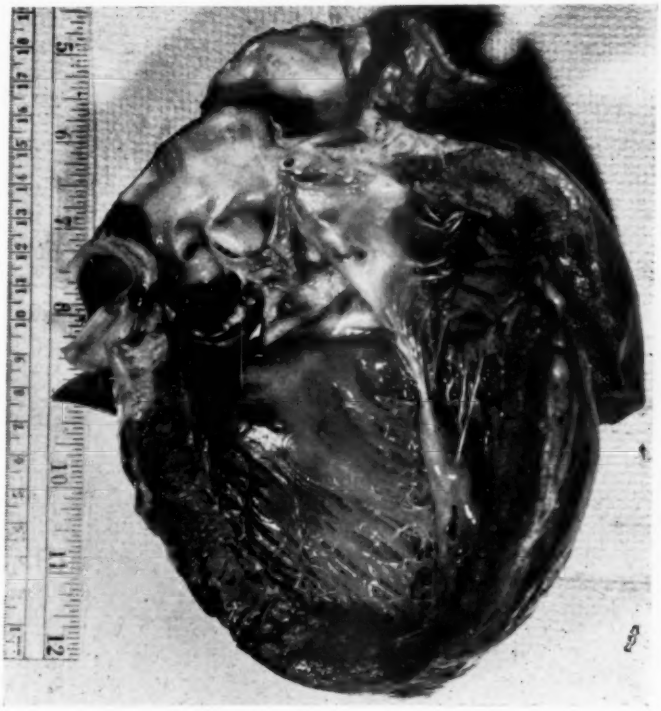

Fig. 3.—The depth of sacculation of the right cusp and its thickened free margin are shown in contrast to the normal middle cusp.

right cusp of the aortic valve. The aorta was dextroposed slightly, overlapping the right ventricle by about 4.0 mm., a slight fold connecting the edge of the aortic wall with the ventricular septum lateral to the defect. The defect paralleled the base of the right aortic cusp, and was roughly crescent shaped, measuring 2.0 cm. by 0.6 cm. (Figs. 2 and 3). The left and middle aortic valve cusps were normal, but the right cusp was markedly roughened and calcific on its free border to such an extent that the cusp was held rigidly away from the aortic wall. The base of the cusp was dilated, forming a slightly trabeculated sac measuring about 1.8 cm. in diameter (shown best in Fig. 3). On depressing the calcified saclike cusp, the septal defect appeared to be effectively closed. The orifices of the coronary arteries were higher than usual, being at a level with the upper borders of the aortic cusp. The aortic valve ring measured 9.0 cm. in circumference.

The middle cusp of the pulmonic valve was slightly asymmetrical on its left border. This defect was apparently caused by a saclike invagination into the interventricular septum at this point in an area measuring 1.5 by 0.8 centimeter. This was lined with endocardium and several strands of muscle covered by endocardium extended across it. A probe could be directed inferiorly into the defect for a distance of 1 cm., where the sac ended blindly. The pulmonic valve ring measured 8.5 cm. in circumference. The other valves appeared to be normal except for slight thickening of the points of closure of the mitral valve.

Pathologic Diagnosis.—(1) Congenital heart disease (Eisenmenger Complex, mild). High ventricular septal defect; slight dextroposition of the aorta; deformity and calcific changes in the right aortic cusp; moderate enlargement of the pulmonary artery. (2) Absence of the ligamentum arteriosus.

REMARKS

The extent of dextroposition of the aorta was so slight that it was only recognized on close re-examination and the pathologic physiology which resulted from this defect was, therefore, about that which would have resulted from a large, high ventricular septal defect rather than that which would have resulted from a severe grade of the Eisenmenger complex.

It is evident from the specimen that in diastole the sacculated cusp was carried down into the ventricle to partly stopper the interventricular defect and to leave the aortic valve incompetent; while in systole the enlarged cusp with its rigid free margin was flung into the lumen of the aorta and, unable to collapse against the wall, partially obstructed this vessel.

It is felt that the changes found in only the right aortic cusp, which are seen in lesser degree in simple high ventricular septal defects as well as in the Eisenmenger complex, were slowly acquired as a result of trauma from unusual motion of the cusp, and its unusual exposure to blood currents. The slow progression of these changes in the cusp probably gave rise to the murmurs of aortic insufficiency and aortic stenosis which were noted late in the course of the disease, and which were attributed clinically to acquired rheumatic aortic valvular disease. (Abbott[1] found acquired valvular disease of a chronic nature in fourteen of fifty cases of simple interventricular septum defect.)

The diastolic element of the continuous machinery-like murmur and thrill which led to the clinical diagnosis of patent ductus arteriosus may have originated in the asymmetric middle cusp of the pulmonic valve and the adjacent saclike invagination into the interventricular septum. (Abbott suggested that the diastolic element of the murmur in patent ductus was that of a pulmonary insufficiency.)

Absence of the ductus arteriosus, as a complication of other congenital defects, was noted by Abbott in fifteen of her 1,000 cases. In this case, it is interesting to consider the possible relationship of the absent ductus arteriosus in fetal life to the persistency of the interventricular septal defect.

Aside from the "pathognomonic" thrill and murmur, the other clinical findings appeared, after careful and prolonged study, to fulfill the generally accepted criteria for the presence of a patent ductus arteriosus. It seems probable that only right heart catheterization and demonstration of arterialization of right ventricular blood would have established clinically and preoperatively the presence of the high ventricular septal defect.

SUMMARY

(1) A case of high ventricular septal defect with slight dextroposition of the aorta and deformity of the aortic valve (Eisenmenger Complex), which presented the clinical features of patent ductus arteriosus, is reported.

(2) It is suggested that only right heart catheterization might have established the presence of the septal defect ante mortem.

REFERENCES

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Abstracts and Reviews

Selected Abstracts

Thordarson, O.: Clinical Study on the Relative Incidence of Congenital Heart Disease, Acta med. Scandinav. **127**:233, 1947.

Of 4,746 patients suffering from cardiovascular diseases, eighty-five (0.27 per cent) presented signs and symptoms of congenital heart disease, forty-eight cases of which were proved at necropsy. Sixty-four were older than 15 years when first examined, and 75 per cent had no apparent impairment of cardiac function.

HECHT.

Nylin, G., and Biorck, G.: Circulatory Corpuscle and Blood Volume in a Case of Patent Ductus Arteriosus Before and After Ligation, Acta med. Scandinav. **127**:434, 1947.

Blood volume determination with radioactive phosphorus in one patient revealed 1,491 Gm. of circulating red cells before, and 1,365 Gm. after operation, a reduction of 8 per cent. The total circulating blood volume decreased from 4,086 to 3,593 ml., a reduction of 12 per cent.

HECHT.

Espersen, T., and Jorgensen, J.: Electrocardiographic Changes in Paroxysmal Hypertension Due to Chromaffin Adrenal Tumor, Acta med. Scandinav. **127**:494, 1947.

Before operation, sixteen electrocardiograms were recorded, three tracings during an attack and the remainder in the interval periods. Normal findings alternated with sinus tachycardia, auricular fibrillation, auricular flutter, and sinoauricular block. During the episodes of hypertension, auricular fibrillation was observed twice and A-V block with ventricular escape, once. Following removal of the tumor, a period of auricular fibrillation was present which was soon followed by a normal sinus mechanism. The case is described in detail in *Acta chirurgica Scandinavica* **94**:271, 1946.

HECHT.

Cantonnet, P., and Milovanovich, J. B.: Two- and Three-Dimensional Electrovectography in Man, Compt. rend. Soc. de biol. **141**:613 (June), 1947.

A method is described which combines conventional electrocardiography and vectorcardiography by recording the image of the vectorcardiogram on a moving film (5.0 mm. per second). Simultaneously recording the vectorcardiograph of the frontal and of the anteroposterior plane permits a three-dimensional concept of the distribution of the action current. It is postulated that the method provides information not obtainable by the conventional methods. No pertinent examples are given.

HECHT.

Franck, C., Grandpierre, R., Lemaire, R., and Auscher, C.: The Effect of Anoxia on Adrenalin Induced Hyperglycemia, Compt. rend. Soc. de biol. **141**:776 (July), 1947.

The rise in blood glucose that follows the administration of 0.04 mg. per kilogram of body weight of epinephrine is inhibited in anesthesized dogs which are made to breathe 7 to 10 per

cent oxygen in nitrogen. This diminished response of the anoxic animals to epinephrine is comparable to the previously observed decreased increment in systolic and diastolic blood pressure following epinephrine under similar conditions. The details of the procedure are not given.

HECHT.

Lian, C., Lavenne, F., and von Roten, L.: An Exercise Test in Obliterating Arterial Disease, Arch. d. mal. du coeur **40**:273 (July-Aug.), 1947.

The influence of a standard exercise test on the arterial pressure and oscillometric indices of an extremity was determined in twenty normal subjects, in twenty-five patients with obliterating arterial disease, and in four with coarctation of the aorta. The test consists in running movements while standing for one minute or until pain occurs (lower extermities), or in raising the hand vertically to shoulder height thirty times in one minute (upper extremity).

In the normal subjects, a moderate increase in blood pressure, usually not exceeding 10 mm. Hg, is noted together with a definite increase in the oscillometric indices. In seventeen of twenty-five patients with arterial diseases, a fall in pressure and a decrease in oscillations were observed. A similar response was obtained in two of the four patients with coarctation of the aorta. It is assumed that the abnormal reactions are the result of insufficient irrigation of the involved limbs, which in turn is followed by local vascular spasm. The test may have diagnostic and prognostic implications.

HECHT.

Mathieu, L., and Hadot, E.: Obliterating Arterial Disease of the Upper Extremity Following Severe Urticaria, Arch. d. mal. du coeur **40**:326 (July-Aug.), 1947.

A 44-year-old white collar worker developed extremely severe pain with absence of pulse and oscillometer readings and with loss of color of the left forearm and hand sixteen hours after a severe and unexplained attack of urticaria. Treatment with periarterial injections of novocain and repeated intra-arterial injections of Priscol restored circulation through the affected limb only partially. From the findings, an organic arterial occlusion of the limb is assumed to have occurred, and it is argued that a causal relationship existed between the accident and the urticarial reaction. The patient exhibited no signs or symptoms of vascular disease before the accident.

HECHT.

Mathieu, L., and Hadot, E.: Myocardial Infarction and Angina Pectoris During Serum Sickness, Arch d. mal. du coeur **40**:328 (July-Aug.), 1947.

A 40-year-old metal worker developed a severe general illness with precordial pain within twenty-four hours after an injection of antitetanus serum. The electrocardiogram revealed a recent posterior myocardial infarction. The patient had received three previous injections of antitetanus serum; the last two were complicated by serum sickness. A second patient, a 61-year-old man, also developed typical "accelerated" serum sickness with severe precordial pain, but without evidence of infarction within forty-eight hours after a similar serum injection. This patient had also been previously sensitized. An anaphylactic reaction of the coronary arteries is implicated.

HECHT.

Cournand, A., Motley, H. L., Himmelstein, A., Dresdale, D., and Baldwin, J.: Recording of Blood Pressure From the Left Auricle and the Pulmonary Veins in Human Subjects With Inter-auricular Septal Defects, Am. J. Physiol. **150**:267 (Aug.), 1947.

Mean auricular pressures in three infants with interauricular septal defects were measured by venous catheterization. The average right auricular pressures averaged 1.4 mm. Hg; left auricular pressures, 4.1 mm. Hg; and pressures in the pulmonary vein, 6.2 mm. of mercury. The right ventricular pressures were elevated in all patients. The amplitude of the pulse curve was

considerably larger in the left than in the right auricle. It is postulated from these observations that in normal man the dynamic conditions within the auricular cavities may differ to a considerable extent.

HECHT.

Motley, H. L., Cournand, A., Werko, L., Himmelstein, A., and Dresdale, D.: The Influence of Short Periods of Induced Acute Anoxia Upon Pulmonary Artery Pressure in Man, Am. J. Physiol. **150:**315 (Aug.), 1947.

Five normal subjects were allowed to breathe 10 per cent oxygen in nitrogen for ten minutes during venous catheterization. Oxygen saturation of arterial blood decreased from 94.5 to 73.4 per cent; cardiac output, from 5.74 to 5.20 liters per minute. Pressures in the pulmonary artery increased from 13.1 to 23 mm. Hg; in the right ventricle, from 7.9 to 14 mm. of mercury. The pulmonary resistance increased markedly from 130 to 255 dynes cm.$^{-5}$. The transient pulmonary hypertension and the increase in pulmonary resistance may have been caused by vasoconstriction of the pulmonary arterioles or precapillaries, or by stasis of the smaller pulmonary vessels inaugurated by altered capillary permeability. Hyperventilation and alkalosis seem to play no part in the changes observed.

HECHT.

Stickney, J. C., Northrup, D. W., and van Liere, E. J.: Systemic Blood Pressure as a Factor in the Absorption of Saline From the Small Intestine, Am. J. Physiol. **150:**466, (Sept.), 1947.

Absorption of saline from the small intestine may be accomplished by increasing the area of the capillary bed concerned with fluid transport by raising the infusion pressure through the circulatory system. The rate of absorption may be decreased by producing congestion of the mesenteric veins. If in dogs arterial pressure is lowered by carotid sinus stimulation, absorption of fluid and chlorides is not greatly altered. However, a statistically greater removal of saline from the gut was observed in dogs whose blood pressures ranged from 150 to 190 as compared with the absorption of solutes in normotensive animals. This may have been caused by greater than usual pressures in the arteriolar end of the capillaries and/or by the opening up of more active capillaries causing an increase in circulation of extracellular fluid in the active region of the mucosa.

HECHT.

Guest, M. M., Murphy, R. C., Bodnar, St. R., Ware, A. G., and Seegers, W. H.: Physiological Effects of a Plasma Protein: Blood Pressure, Leucocyte Concentration, Smooth and Cardiac Muscle Activity, Am. J. Physiol. **150:**471, (Sept.), 1947.

The plasma fraction carrying fibrinolysin exhibits potent depression of blood pressure and cardiac output in turtles, rabbits, guinea pigs, and dogs. The fraction produced leucopenia within three minutes after its injection and appears to increase tonus and amplitude of isolated intestinal muscle strips. The plasma fraction exhibits this pharmacologic activity even after fibrinolysin has been inactivated or destroyed. A new plasma factor, termed vascularin, is implicated.

HECHT.

Harris, A. S., and Matlock, W. P.: The Effects of Anoxemic Anoxia on Excitability, Conduction and Refractoriness of Mammalian Cardiac Muscle, Am. J. Physiol. **150:**493 (Sept.), 1947.

A number of fundamental properties of heart muscle in dogs were evaluated during gradually increasing degrees of anoxia induced by a simple, accurate rebreathing apparatus. During mild anoxia, excitability, conduction rate, and the refractory period shortened to a considerable degree. Severe anoxia caused the usual decrease in excitability and lengthening of the conduction rate. No ventricular extrasystoles occurred at any time during the anoxic period.

HECHT.

Wilburne, M., Schlichter, J. G., Grossman M., and Cisneros, F.: The Use of Acetyl-Choline in the Objective Determination of Circulation Time and the Fractionation of the Vascular Bed Traversed, Am. J. Physiol. **150**:504 (Sept.), 1947.

Transitory inhibition of the sinus node or the A-V junctional tissue in dogs occurred five to eight seconds (average 6.7 seconds) after the injection of 0.02 to 0.5 ml. of a 5 per cent solution of acetylcholine chloride. When acetylcholine is injected into various parts of the vascular system, end points are obtained only when the coronary circulation is included in the pathway. Clamping the right coronary artery abolishes the end point. Evidence is presented which implicates the sinus node as the effector site.

HECHT.

Hansen, P., and Faber, M.: Raynaud's Syndrome Originating From Reversible Precipitation of Protein, Acta med. Scandinav. **129**:81 (Oct.), 1947.

A 47-year-old unmarried woman was observed to suffer from a Raynaud-like syndrome. She died eighteen months later of aleucemic plasma cell leucemia. The attacks, which were strictly localized to the parts of the body that were exposed to cooling and not only the fingers, invariably occurred upon exposure; they never disappeared spontaneously, but only upon application of heat. Her condition grew steadily worse, so that during the last six months the patient had to be fully covered at all times and required almost continuous warm baths of her body and fingers. A thrombosis of the central retinal vein finally complicated the syndrome.

The patient's serum or plasma congealed readily when exposed to room temperature. It is shown that this was caused by precipitation of an abnormal protein that could be demonstrated in the patient's blood. It had the properties of gamma globulin (euglobulin) and could be precipitated quantitatively by 40 per cent saturated ammonium sulfate. It was not amyloid and did not contain sulfur. Its solubility at 40° C. in normal saline was 3.3 per cent; at 30° C., only 0.05 per cent.

In this patient the demonstration that the flow of blood through the fingers ceased during attacks while the pulse volume remained unaltered argues strongly in favor of an in vivo precipitation of this protein as the cause of Raynaud's syndrome. Had the attacks been caused by local vasoconstriction, plethysmographic observations should have revealed a reduction in both volume-flow and in pulsation.

Total serum protein, serum albumin, and serum globulin collected at room temperature measured 6.7, 5.2, and 1.5 Gm. per 100 c.c., respectively. The same values when collected at 40° yielded 8.16, 3.96, and 4.2 Gm., respectively. (The properties of the protein closely resemble those described recently by Lerner and Watson as "cryoglobulin.")

HECHT.

Eyster, J. A. E., and Gilson, W. E.: Electrical Characteristics of Injuries to Heart Muscle, Am. J. Physiol. **150**:572 (Oct.), 1947.

Voltage, current flow, and impedance were measured from injured regions of ventricular muscle of dogs and turtles using a cathode ray oscillograph with varying resistances across the input leads of the amplifier. When the decrease in resistance across the input leads is known, current flow and impedance may be calculated from the values of the voltages recorded. Decisive changes in voltage, current, and impedance occur over the injured region which are dependent on the activity of the muscle surrounding the injured area.

HECHT.

Spealman, C. R., Newton, M., and Post, R. L.: Influence of Environmental Temperature and Posture on Volume and Composition of Blood, Am. J. Physiol. **150**:628 (Oct.), 1947.

Two subjects were exposed to six-day periods of uncomfortably warm (91° F. dry bulb, 82° F. wet bulb) and uncomfortably cold (69° F. dry bulb, 60° F. wet bulb) temperatures. The temperatures were altered from warm to cold to warm during a summer experiment and from cold

to warm to cold during a winter experimental period. Blood volumes were calculated by a carbon monoxide method combined with estimation of the volume of packed red cells. During both experimental periods total circulating hemoglobin changed little and the alterations observed indicated a change in plasma volume alone. It increased during exposure to prolonged heat and decreased in cold environment. Diurnal variation in plasma volume is presumably dependent on posture. A recumbent position favors an increase in the volume of circulating plasma; upright posture decreases plasma volume.

HECHT.

Hernberg, C. A.: Myocardial Affection in Malaria Tertiana, Acta med. Scandinav. **129**:132 (Nov.), 1947.

Six of 596 patients suffering from malaria were observed to complain of stenocardia, palpitation, and rapid heart action occurring usually two weeks after the termination of the attack by acridine-plasmochin treatment. At the time of the complaints the patients did not receive antimalarial medication. In one patient treated with quinine only, a pancarditis with cardiac enlargement was suspected. Electrocardiograms during this period revealed minor changes in the S-T segment and the T wave.

HECHT.

Ravich, R. M., and Rosenblatt, P.: Myocardial Infarction in the Newborn Infant. Am. J. Pediat. **31**:266 (Sept.), 1947.

Two instances of myocardial infarction in newborn infants, 2 days and 10½ hours of age, respectively, are described. The authors felt that the probable pathogenesis in the first case was intrauterine infection of long standing which affected the small arteries of the heart and lung and also resulted in fibrosing pancreatitis. The second infant had a very recent hemorrhagic infarct. The Rh studies were negative, and there were no other manifestations of hemorrhagic disease of the newborn. Other etiological possibilities suggested are: The pressor fraction of the pituitary extract may have caused excessive constriction of the coronary vessels; cranial trauma may have caused an increase in intracranial pressure and secondary vasoconstriction; direct trauma to the precordium must be considered.

HAUB.

Kagan, B. M., and Mirman, B.: Sydenham's Chorea, a Syndrome for Differential Diagnosis. Am. J. Pediat. **31**:322 (Sept.), 1947.

This study was made in order to investigate the differences between chorea with a normal sedimentation rate and chorea with an increased rate. Chorea associated with an increased sedimentation rate was found to be a manifestation of active rheumatic fever in 84 per cent of cases. Patients with chorea and a normal sedimentation rate during their first episode of chorea do not have rheumatic fever and are no more subject to its sequelae than are other members of the population. Psychogenic factors were much more common in cases of nonrheumatic chorea.

Recurrences of chorea were found in 24 per cent of patients with rheumatic chorea and in only 6 per cent of those with the nonrheumatic type. Recurrences among patients with nonrheumatic chorea were always nonrheumatic. However, among forty-eight patients with rheumatic chorea there were four recurrences that were not associated with any evidence of rheumatic activity. The etiology of nonrheumatic chorea has not been established, but the frequency of emotional disturbance suggests that psychogenic factors are important and that modern psychotherapeutic approach may yield practical results.

HAUB.

Feuchtwanger, J. L.: Arteriography of the Limbs. Brit. J. Radiol. **20**:363 (Sept.), 1947.

The author presents a technique for arteriography of the limbs based upon prolonged exposure time. Emphasis is placed on the fact that this is not a routine procedure but is most

useful in cases where the clinical diagnosis of a vascular lesion is uncertain or the exact localization is required.

In all cases in which the lower limbs were studied, a surgical exposure, in Scarpa's triangle (for femoral profunda) or in Hunter's canal (for popliteal artery), was carried out under local anaesthesia. The vessel was compressed proximal to the site of injection.

Ten cubic centimeters of Diodon (70 per cent) were introduced into the artery through a 19 guage needle over a period of about three seconds. Sensitivity was tested either by the dermal or occular procedure prior to the injection. Two films were exposed for each view and at least two views were taken. The first exposure was taken immediately after the completion of the injection and the second as soon thereafter as possible. A separate injection was made for each view.

A similar method was used for the brachial artery. A sphygmomanometer cuff was used for vascular compression. Injections of 5 to 8 c.c. of the opaque material usually were sufficient for adequate arterial visualization. Five illustrative cases of aneurysms with the described techniques being used are presented.

In order to obtain maximum filling of an aneurysmal sac and demonstration of the collaterals in the region of the vascular lesion, the exposure time was prolonged from three to six seconds. This varied according to the thickness of the part and the milliamperage used. The kilovoltage varied from 55 to 60 and the milliamperage from 5 to 15, the milliampere-seconds being the same as in ordinary radiography.

No serious reactions to the opaque material were encountered by the author.

ZION.

Stadie, W. C., and Marsh, J. B.: The Effect of Cytochrome C Upon the Metabolism of Rat Tissue. J. Clin. Investigation **26**:899 (Sept.), 1947.

Proger has reported that changes due to anoxia (visual changes, electrocardiographic alterations, etc.) were prevented by antecedent injections of cytochrome C. He postulates that anoxia is associated with a relative decrease of cytochrome C compared to cytochrome oxidase.

The authors confirm the observation of Proger that adenosine triphosphate content of anoxic rat kidney is decreased. However, the prevention of this decrease of adenosine triphosphate by antecedent intravenous administration of cytochrome C was not observed. No alteration in oxygen consumption of rat liver or kidney slices was observed in vitro following the addition of cytochrome C. to the medium.

WAGNER.

Munnell, W. E., and Taylor, H. C.: Liver Blood Flow in Pregnancy—Hepatic Vein Catheterization. J. Clin. Investigation **26**:952 (Sept.), 1947.

Most investigators agree that there is some disturbance of liver function in toxemia of pregnancy. Direct sampling of blood leaving the liver by venous catheterization offers further opportunity for study of liver function.

Hepatic blood flow was estimated by the Fick principle using bromsulfalein as a test substance. It might have been expected that the hepatic blood flow would be increased because of the increased blood volume of pregnancy. However, it was found that hepatic blood flow does not differ in normal uncomplicated pregnancy from that of normal nonpregnant patients. The liver blood flow remains unchanged in the presence of an increased blood volume.

WAGNER.

Taussig, Helen B.: Diagnosis of the Tetralogy of Fallot and Medical Aspects of the Surgical Treatment. Bull. N. Y. Acad. Med. **23**:705 (Dec.), 1947.

This pathological entity is defined and the physical, x-ray, and electrocardiographic features described. Since the operation is best carried out on the opposite side to that upon which the aorta arches, it is important to determine the position of the aortic arch preoperatively. A right aortic arch occurs in 20 to 25 per cent of all cases of tetrology of Fallot.

The operation is briefly described and the advantages of an end-to-side anastomosis are stressed. This procedure is best performed between the ages of 2 and 15 years. Indications vary with age of the patient and depend upon the severity of the pulmonary stenosis and upon the height of the compensatory polycythemia.

Pre- and postoperative care are discussed as well as the management of complications. The latter include cerebral thrombosis, pleural effusion, pneumothorax, cardiac failure, and suppression of renal function and thrombosis at the site of the anastomosis.

The results of the first 300 operations are as follows: 18 per cent have died during operation or shortly afterward; 3 per cent were found to be inoperable but survived an exploratory thoracotomy; 3.5 per cent were unimproved by operation; 4.5 per cent were helped but not brilliantly improved; 71 per cent were greatly benefited by operation.

WOODS.

Beck, C. S., Pritchard, W. H., and Feil, H. S.: Ventricular Fibrillation of Long Duration Abolished by Electric Shock. J. A. M. A. 135:985 (Dec. 13), 1947.

The authors report the first case with complete recovery after prolonged ventricular fibrillation. A boy, 14 years of age, was admitted to the hospital for sternal resection because of a severe congenital funnel chest. The only symptom was dyspnea on effort, gradually increasing for two years preceding his admission to the hospital. During closure of the wound in the chest, the pulse suddenly stopped and the blood pressure sounds could not be heard. The wound was reopened and cardiac massage immediately initiated; 1.0 mg. of epinephrine was given intravenously and lanatoside C was also administered without visible results. The mechanical respirator was then attached to the intratracheal tube and cardiac massage continuously given for the next thirty-five minutes, at the end of which time the electrocardiogram was characteristic of ventricular fibrillation. Another record made ten minutes later was recorded just prior to the first electric shock applied directly to the heart. This record as well as the tracing recorded immediately after the first shock also showed ventricular fibrillation. After a second series of shocks were given, feeble, regular, and fairly rapid cardiac contractions were seen, but massage was continued for five minutes more at which time the contractions became coordinated and fairly vigorous though still rapid. An electrocardiogram at this time revealed a supraventricular tachycardia with a rate of 175. From this point on, the action of the heart gradually increased in vigor and brachial sounds were heard at 50 mm. of mercury. After the coordinated heart beat had been established for twenty minutes the wound in the chest was closed. Three hours after defibrillation of the ventricles, the patient responded rationally to questioning and soon became fairly alert. Three months later electrocardiographic tracings were normal.

BELLET.

Dresbach, M.: Further Experiments in an Attempt to Locate the Site of the Emetic Action of the Digitalis Glycosides. J. Pharmacol. & Exper. Therap. 91:307 (Dec.), 1947.

The emetic dosage of purified digitalis glycosides was first determined in animals preoperatively. The animal was then subjected to painstaking collective visceral differentiation (vagotomy and low cervical cordotomy). Ample time for postoperative recovery was allowed, and when the animal was in statu quo, the same drugs were again administered. There was no significant variation in the emetic action of the glycosides in the same animal pre- and postdifferentiation. This is further evidence that the emetic action of the digitalis-like glycosides is central in origin.

GODFREY.

Eckenhoff, J. E., Hafkenschiel, J. H.: The Effect of Nikethamide on Coronary Blood Flow and Cardiac Oxygen Metabolism. J. Pharmacol. & Exper. Therap. 91:362 (Dec.), 1947.

Using anesthetized, intact, spontaneously breathing specimens, the authors measured coronary blood flow with the bubble flowmeter. Nikethamide (Coramine) was tested first in doses

comparable to those used in man. No demonstrable increase in coronary blood flow occurred. The same technique being used, consistant increase in coronary blood flow occurred with both papaverine and theophylline ethylenediamine. It is interesting to note that no consistent changes in blood flow could be demonstrated with either nitroglycerin or amyl nitrite.

With higher dosage of nikethamide there was a rather marked increase in coronary flow; however this was accomplished at the expense of cardiac efficiency. There was a disproportionate increase in oxygen uptake for the amount of work performed. At such dosage levels, restlessness, convulsions, and death were common, suggesting that the dosage necessary to produce these effects was markedly toxic. The evidence available fails to support the use of Coramine as a "cardiac tonic."

GODFREY.

Maliner, M. M., and Amsterdam, S. D.: Oral Penicillin in the Prophylaxis of Recurrent Rheumatic Fever. J. Pediat. 31:658 (Dec.), 1947.

Penicillin troches were administered to twenty-two rheumatic children during the fall, winter, and spring seasons of 1945 to 1946 and 1946 to 1947. During the first half of the study, troches containing 1,000 Oxford units of penicillin were used; during the second half of the work, troches containing 5,000 units were employed. The patients were advised to suck each troche for one hour after each meal. The authors feel that penicillin has two advantages over sulfa drugs in the prophylaxis of rheumatic fever: (1) the therapeutic agent acts directly upon the focus of infection rather than requiring a definite blood level to achieve the necessary effect; (2) repeated leucocyte, hemoglobin, differential counts, and urinalysis are not required. None of the twenty-two children receiving penicillin lozenges developed definite attacks of acute rheumatic fever. Four of the control group developed acute attacks.

HAUB.

Rogers, J., and Robbins, S. L.: Latent Rheumatic Myocarditis. New England J. Med. 237:829 (Dec.), 1947.

Active rheumatic myocarditis was correctly diagnosed clinically in less than half of a series of forty-one consecutive cases in which this diagnosis was proved pathologically. The average age was 18 years in the twenty patients diagnosed correctly in life. In contrast, the average age was 53 years in the twenty-one clinically undiagnosed cases. In ten of the latter, the terminal cardiac failure was attributed to the mechanical strain of rheumatic valvular deformity. In retrospect, major or minor manifestations of rheumatic activity had been present in eight of these ten patients. In an additional seven patients, rheumatic heart disease had been completely unsuspected clinically, and although all showed evidences of healed or active valvulitis, characteristic manifestations of rheumatic activity had been singularly absent during life. In the remaining four cases, active myocarditis was an incidental finding, unsuspected clinically, and unassociated with clinical rheumatic manifestations or with pathologic evidences of endocarditis or pericarditis.

The authors attribute the infrequency of correct clinical diagnosis of active rheumatic myocarditis in older patients to several factors: The active carditis often assumes an atypical form in which the diagnosis of activity may depend upon careful evaluation of isolated rheumatic manifestations; other diseases may appear to provide an adequate basis for the clinical findings and thereby obscure the diagnosis; and occasionally the myocarditis is completely unaccompanied by other rheumatic manifestations which might provide a clue to the etiology. Cardiac decompensation in rheumatic heart disease, even in older persons, is frequently the result of activity of the disease.

KAY.

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JOURNAL MEMBERSHIP RATE INCREASED

Effective July 1, the annual Journal membership rate is increased from $10 to $12 per year. Six-month Journal memberships are advanced from $6 to $8. Those already holding annual Journal memberships for 1948 will not be affected by the increase until Jan. 1, 1949.

REPORTS OF LOCAL HEART ASSOCIATION ACTIVITIES

The part played by local heart associations before, during, and after National Heart Week in helping to assure the success of the national campaign is illustrated in the following reports from New York, Chicago, and Boston.

New York Heart Association.—Between January 1 and April 30, 1948, the New York Heart Campaign raised $573,620, 114 per cent of its $500,000 goal, to support the 1948 program of the New York Heart Association. The amount raised this year was more than two and one-half times the funds collected in 1947. Contributions included 13,500 separate, recorded gifts plus thousands more obtained through mass collection devices. A working force of over 2,500 volunteers assisted in fund-raising.

Carl Whitmore, president of the New York Telephone Company, served as chairman of the campaign. He enlisted division chairmen from among business and civic leaders to direct the efforts of voluntary workers in business and home communities. Seventy-five full-time volunteers were obtained on loan from banks, insurance companies, utilities, and business firms. These volunteers carried on the work of the business division.

For the solicitation of advance gifts, Mr. Whitmore received the active aid of the officers and directors of the New York Heart Association.

The entertainment industry was mobilized by Mrs. Arthur Baer, wife of "Bugs" Baer, noted newspaper humorist, and Ed Sullivan, Broadway columnist, both of whom are members of the New York Heart Association Board of Directors.

The New York campaign started with the proclamation of a "Cardiac Crusade" by Mayor William O'Dwyer. New Yorkers were called on through coupons and announcements in newspapers as well as radio transcriptions and spot announcements to write to the mayor offering their services as volunteers in the local campaign. At the conclusion of the campaign, more than ten times as many workers had been enlisted and six times as many gifts obtained as in 1947.

Many special events, radio programs, television shows, and news-creating promotions were arranged. These included the following:

The Mark Hellinger Memorial Fund was formed by his colleagues and friends to honor the film producer who died of a heart attack. The principal activity was the world premier of Hellinger's last picture "Naked City." From the sale of seats ($5 to $500 each) and advertisements in a souvenir program, $150,000 was raised.

Comedian Milton Berle broadcast for twenty-four consecutive hours over Station WHN, introducing guest stars and appealing for contributions. Night clubs participated in the campaign, with "Heart Night" observed at the Copacabana and an "Easter Brunch" held at the Monte Carlo. A Broadway concert by Maurice Chevalier and a performance of the play, "Mr. Roberts," both served as benefit events. The chain of thirty Skouras theaters in the New York metropolitan area relaxed a ban against audience collections and set aside ten days for fund-raising. Variety shows, fashion shows, quiz programs, auctions, and other campaign events were televised.

Chicago Heart Association.—The 1948 fund-raising campaign of the Chicago Heart Association is more than halfway toward its goal of $200,000. The campaign was inaugurated during National Heart Week with a dinner on February 10 at the Union League Club, attended by 200 business and civic leaders, including Mayor Kennelly, and distinguished members of the medical profession. Speakers were Dr. Arlie R. Barnes, Dr. Howard A. Rusk, and Dr. Wingate M. Johnson, with Dr. Morris Fishbein as toastmaster. Exhibits, including seven hearts of Chicago business leaders who died of heart disease and an isolated beating rabbit heart, attracted a good deal of attention.

This was the first large-scale campaign undertaken by the Chicago Heart Association. Mr. S. DeWitt Clough served as chairman. Various techniques were tried, with a view to developing a fund-raising pattern which can be followed on a larger scale in the future.

The Valentine seal sale, which has been the chief source of revenue of the Chicago Heart Association in previous years, was continued. During January, letters enclosing two books of 100 seals each were sent to more than 68,000 prospects. This brought in a total of more than $36,000. In addition, a Special Gifts committee was active in soliciting funds. Appeal letters with pamphlet enclosures were circulated among thousands of individuals and corporations. The benefit premiere of the film, "Casbah," with a special stage presentation including Hollywood and night club celebrities, raised almost $10,000. A fourteen-hour marathon broadcast by Milton Berle over Station WIND brought in pledges of more than $31,000. The number of memorial contributions was greatly increased during the campaign.

Active cooperation of community organizations was enlisted: for example, the Service Club of Chicago underwrote the salary of an occupational therapist employed by the Chicago Heart Association to work with homebound cardiac children.

The wide publicity during the Chicago campaign was important for its educational as well as its fund-raising value. One of the events notable for its educational aspects was the University of Chicago Round Table broadcast over the NBC network. Participants included Doctors George K. Fenn, Louis N. Katz, Emmet B. Bay, and Stanley J. Gibson, all officers of the Chicago Heart Association.

New England Heart Association.—In its first general educational and fund-raising program, the New England Heart Association collected $44,000. The Association made a rather late start in its organizational activities in Boston, because it was awaiting the outcome of discussions with the Community Fund. Many other large cities in New England cooperated in the campaign, yielding $11,000 to the total.

Bradley Dewey, prominent industrialist and scientist of Cambridge, Mass., served as chairman of the campaign. Mrs. William Brace Pratt, of Milton, Mass., was chairman of the Boston committee.

Special emphasis was placed on the use of plastic heart collection boxes. The Association negotiated with the wholesale and retail drug industries and their state association for the display of plastic hearts in all drugstores.

Many fifteen-second radio spots, having as their principal message "Give at your local drugstore," supplemented the longer statements supplied for the national campaign. Physician members accepted assignments for radio and newspaper interviews. Publicity photos included professional models posed with child victims of rheumatic fever. The direct mail campaign included hand-signed personalized letters as well as multigraphed appeals.

In Boston, the Association received $5,000 in unsolicited gifts. The plastic heart yield is eventually expected to total $7,000. A total of $3,000 was received in memorial gifts.

CHANGES IN CERTIFICATE OF INCORPORATION

Proposed changes in the Certificate of Incorporation of the American Heart Association were submitted to the members at the Annual Meeting in Chicago in June. The new statement of purposes and objectives of the Association reads as follows:

"The purposes for which it is formed are the study of and the acquisition, dissemination and application of knowledge concerning the normal heart and circulation and the causes, diagnosis, prevention, and treatment of disorders of the circulation and diseases of the heart, blood vessels

and lymph vessels; the development and application of measures that will prevent such disorders and diseases; the gathering and publication of information upon all aspects of such disorders and diseases, including studies of occupations suitable for patients with diseases or disorders of the heart or circulation; the encouragement of the establishment of special dispensary facilities for patients with such diseases, and of facilities for adequate convalescent care of such patients, and the promotion of permanent institutional care for such of them as are hopelessly incapacitated for self-support; and the encouragement, establishment and assistance of local associations and committees with similar purposes, or one or more thereof, in such cities, states or regions as the Board of Directors shall determine, throughout the United States and Canada. Nothing herein contained shall authorize the corporation to establish or maintain any hospital, infirmary, dispensary, clinic, home or institution for convalescent or invalid persons or a hospital service or medical expense or other indemnity plan."

Other changes include the addition of the Dominion of Canada to the territory of operations and the statement that the number of directors be "not less than twenty-four nor more than forty."

POSTGRADUATE COURSE IN ELECTROCARDIOGRAPHY

The Michael Reese Hospital Postgraduate School in Chicago announces that its Intensive Postgraduate Course for Graduate Physicians in Electrocardiography will be held August 16 through August 28. Presented by Dr. Louis N. Katz, the course will be open to beginning and advanced students and will include group and individual instruction. The tuition fee is $150 and the size of the class is limited. Interested physicians should address Dr. Samuel Soskin, Dean, Michael Reese Hospital Postgraduate School, 29th St. and Ellis Avenue, Chicago 16, Ill.